Rheumatology and the Kidney
Oxford Clinical Nephrology Series

Cancer and the Kidney: The frontier of nephrology and oncology, Second Edition
Edited by Eric P. Cohen

Chronic Kidney Disease: A practical guide to understanding and management
Edited by Meguid El Nahas and Adeera Levin

Lupus Nephritis, Second Edition
Edited by Edmund J. Lewis, Melvin M. Schwartz, Stephen M. Korbet, and Daniel Tak Mao Chan

Rheumatology and the Kidney, Second Edition
Edited by Dwomoa Adu, Paul Emery, and Michael Madaio

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Edited by Klaus Olgaard, Isidro B. Salusky, and Justin Silver

Treatment of Primary Glomerulonephritis, Second Edition
Edited by Claudio Ponticelli and Richard J. Glassock
Rheumatology and the Kidney
SECOND EDITION

Edited by
Dwomoa Adu
Paul Emery
Michael Madaio
Preface

Many diseases affect the joints as well as the kidneys. The aetiology of these multisystem diseases includes autoimmunity, virus infection and the complications of drugs. There have been major recent advances in the understanding of the pathogenesis, diagnosis and treatment of these disorders but these are only available in disparate publications. *Rheumatology and the Kidney* brings together internationally recognized experts in a broad range of disciplines who provide a concise update on these disorders in one publication. Areas covered include lupus nephritis, vasculitis, systemic sclerosis, amyloidosis, virus associated disease and the rheumatological complications of renal disease. Other chapters cover amyloidosis and Hepatitis B and C associated systemic disease. Finally there are chapters on the nephrotoxicity of drugs used in the treatment of rheumatologic diseases and also on rheumatologic complications of dialysis and renal transplantation. The book should be useful to rheumatologists and nephrologists and also to internal medicine physicians and trainees who are interested in the management of patients with autoimmune disorders. The book is updated from the previous edition to include sections on new classifications of diseases, as well as information on new treatments.
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>β₂GPI</td>
<td>β₂-glycoprotein I</td>
</tr>
<tr>
<td>6-MP</td>
<td>6-mercaptopurine</td>
</tr>
<tr>
<td>7-OH-MTX</td>
<td>7-hydroxymethotrexate</td>
</tr>
<tr>
<td>AAECA</td>
<td>anti-aortic endothelial cell antibodies</td>
</tr>
<tr>
<td>AAV</td>
<td>ANCA-associated vasculitis</td>
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<tr>
<td>ABD</td>
<td>adynamic bone disease</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin converting enzyme</td>
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<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
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<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
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<tr>
<td>ADAMTS13</td>
<td>a disintegrant and metalloproteinase with a thrombospondin 1-like domain, member 13</td>
</tr>
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<td>AEF</td>
<td>amyloid enhancing factor</td>
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<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AKI</td>
<td>acute kidney injury</td>
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<tr>
<td>ALMS</td>
<td>Aspreva Lupus Management Study</td>
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<td>ALP</td>
<td>alkaline phosphatase</td>
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<td>AN</td>
<td>analgesic nephropathy</td>
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<td>ANA</td>
<td>anti-nuclear antibodies</td>
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<td>ANCA</td>
<td>anti-neutrophil cytoplasm antibodies</td>
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<td>aPL</td>
<td>anti-phospholipid antibodies</td>
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<td>APP</td>
<td>β-amyloid precursor protein</td>
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<tr>
<td>APRIL</td>
<td>A Proliferation-Inducing Ligand</td>
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<td>APOL1</td>
<td>apolipoprotein L1</td>
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<td>APS</td>
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<td>ARA</td>
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<td>ARB</td>
<td>angiotensin receptor blocker</td>
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<td>ART</td>
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<td>AVID</td>
<td>ANCA-associated Vasculitis Instrument of Damage</td>
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<td>AVN</td>
<td>avascular necrosis</td>
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<td>AZA</td>
<td>azathioprine</td>
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<td>BAFF</td>
<td>B cell-activating factor</td>
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<td>BAFFR</td>
<td>BAFF receptor</td>
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<tr>
<td>BCD</td>
<td>B cell depletion</td>
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<td>BCP</td>
<td>basic calcium phosphate crystals</td>
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<td>BEL</td>
<td>belimumab</td>
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<td>BILAG</td>
<td>British Isles Lupus Assessment Group</td>
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<td>BLIPS</td>
<td>British Lupus Integrated Program</td>
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<td>BlyS</td>
<td>B lymphocyte stimulator</td>
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<td>BMD</td>
<td>bone mass densitometry</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>BNP</td>
<td>brain natriuretic peptide</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<td>BVAS</td>
<td>Birmingham Vasculitis Activity Score</td>
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<td>CAPS</td>
<td>cyto pyrin associated periodic syndrome</td>
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<tr>
<td>CCT</td>
<td>controlled clinical trials</td>
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<tr>
<td>CD40L</td>
<td>CD40 ligand</td>
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<td>CDA</td>
<td>Combined Damage Assessment (index)</td>
</tr>
<tr>
<td>CDR</td>
<td>complementarity-determining region</td>
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<tr>
<td>CI</td>
<td>calcineurin inhibitors</td>
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<td>CIPS</td>
<td>calcineurin-inhibitor induced pain syndrome</td>
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<tr>
<td>CK</td>
<td>creatine kinase</td>
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<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
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<tr>
<td>COX</td>
<td>cyclooxygenase</td>
</tr>
<tr>
<td>CPPD</td>
<td>calcium pyrophosphate deposition</td>
</tr>
<tr>
<td>CR</td>
<td>clinical response</td>
</tr>
<tr>
<td>CR</td>
<td>complete renal remission</td>
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<tr>
<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>CsA</td>
<td>cyclosporine A</td>
</tr>
<tr>
<td>Cs</td>
<td>corticosteroids</td>
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<tr>
<td>CSS</td>
<td>Churg–Strauss syndrome</td>
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<tr>
<td>CT</td>
<td>computerized tomography</td>
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<tr>
<td>CTLA</td>
<td>cytotoxic T lymphocyte antigen</td>
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<tr>
<td>CTX</td>
<td>cyclophosphamide</td>
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<tr>
<td>DAF</td>
<td>decay accelerating factor</td>
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<tr>
<td>dcSSc</td>
<td>diffuse cutaneous systemic sclerosis</td>
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<tr>
<td>DEI</td>
<td>Disease Extent Index</td>
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<tr>
<td>DHFR</td>
<td>dihydrofolate reductase</td>
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<td>DILS</td>
<td>diffuse infiltrative lymphocytosis syndrome</td>
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<td>DPA</td>
<td>D-penicillamine</td>
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<tr>
<td>DRA</td>
<td>dialysis-related amyloidosis</td>
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<tr>
<td>DRESS</td>
<td>Drug Rash or Reaction with Systemic Symptoms</td>
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<tr>
<td>dRVVT</td>
<td>dilute Russell’s viper venom time</td>
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<tr>
<td>DTH</td>
<td>delayed-type hypersensitivity</td>
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<tr>
<td>EAV</td>
<td>experimental autoimmune vasculitis</td>
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<td>EBV</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
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<tr>
<td>EIA</td>
<td>enzyme immunoassay</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<tr>
<td>EMC</td>
<td>essential mixed cryoglobulinaemia</td>
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<tr>
<td>ENA</td>
<td>extractable nuclear antigens</td>
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<td>EPZ</td>
<td>epratuzumab</td>
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<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
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<td>ESRD</td>
<td>end-stage renal disease</td>
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<td>ET-1</td>
<td>endothelin-1</td>
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<td>EULAR</td>
<td>European League Against Rheumatism</td>
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<td>FAC</td>
<td>familial amyloid cardiomyopathy</td>
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<td>FAP</td>
<td>familial amyloidotic polyneuropathy</td>
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<td>FDG</td>
<td>fluordeoxyglucose</td>
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<td>FFS</td>
<td>five-factor score</td>
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<td>FGF</td>
<td>fibroblastic growth factors</td>
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<td>FKBP</td>
<td>FK-binding protein</td>
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<td>FMF</td>
<td>familial Mediterranean fever</td>
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<tr>
<td>GAG</td>
<td>glycosaminoglycan</td>
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<tr>
<td>GBC</td>
<td>gadolinium-based contrast</td>
</tr>
<tr>
<td>GBM</td>
<td>glomerular basement membrane</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
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<td>GM-CSF</td>
<td>granulocyte macrophage colony stimulating factor</td>
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<td>GN</td>
<td>glomerulonephritis</td>
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<td>GPA</td>
<td>granulomatosis with polyangiitis</td>
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<tr>
<td>HACA</td>
<td>human anti-chimeric antibodies</td>
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<td>HAQ</td>
<td>Health Assessment Questionnaire</td>
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<tr>
<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
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<td>HBV</td>
<td>hepatitis B virus</td>
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<tr>
<td>HC</td>
<td>hydrocortisone</td>
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<td>HC</td>
<td>hydroxychloroquine</td>
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<td>HCV</td>
<td>hepatitis C virus</td>
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<td>HGF</td>
<td>hepatocyte growth factor</td>
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<td>HGPRT</td>
<td>hypoxanthine phosphorridosyltransferase</td>
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<td>HIVAN</td>
<td>HIV-associated nephropathy</td>
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<tr>
<td>hpf</td>
<td>high-power field</td>
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<tr>
<td>HSP</td>
<td>heat shock protein</td>
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<tr>
<td>HUS</td>
<td>haemolytic uremic syndrome</td>
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<tr>
<td>ICAM-1</td>
<td>intercellular adhesion molecule-1</td>
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<tr>
<td>ICD</td>
<td>immune complex disease</td>
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<tr>
<td>IFN</td>
<td>interferon</td>
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<tr>
<td>Ig</td>
<td>immunoglobulin</td>
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<td>IgAIC</td>
<td>IgA1 immune complexes</td>
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<td>IgAN</td>
<td>IgA nephropathy</td>
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<tr>
<td>IL</td>
<td>interleukin</td>
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<td>IMPDH</td>
<td>inosine monophosphate dehydrogenase</td>
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<tr>
<td>INR</td>
<td>international normalized ratio</td>
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<td>IRG</td>
<td>interferon regulated gene</td>
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<td>ISN/RPS</td>
<td>International Society of Nephrology and the Renal Pathology Society</td>
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<tr>
<td>ISP</td>
<td>immunosuppressives</td>
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<tr>
<td>IUD</td>
<td>intrauterine death</td>
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<td>IUGR</td>
<td>intrauterine growth restriction</td>
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<td>IVIg</td>
<td>intravenous immunoglobulin</td>
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<tr>
<td>LAC</td>
<td>lupus anticoagulant</td>
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<td>Abbreviation</td>
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<td>LC</td>
<td>light chain</td>
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<td>LCDD</td>
<td>light-chain deposition disease</td>
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<td>lcSSc</td>
<td>limited cutaneous systemic sclerosis</td>
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<td>LFA-1</td>
<td>lymphocyte function-associated antigen-1</td>
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<tr>
<td>LHCDD</td>
<td>light- and heavy-chain deposition disease</td>
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<td>lupus nephritis</td>
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<td>microangiopathic haemolytic anaemia</td>
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<td>MBL</td>
<td>mannose-binding lectin</td>
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<td>MC</td>
<td>mixed cryoglobulinaemia</td>
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<td>MCP</td>
<td>monocyte chemoattractant protein</td>
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<td>MDRD</td>
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<td>MHC</td>
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<td>monoclonal immunoglobulin deposition disease</td>
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<td>MMF</td>
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<td>matrix metalloproteinase</td>
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<td>MPO</td>
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<td>magnetic resonance imaging</td>
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<td>periodic acid-Schiff</td>
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<td>PATH</td>
<td>proteinuria, aPL, thrombocytopenia and hypertension</td>
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<td>PCR</td>
<td>protein-to-creatinine ratio</td>
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<td>PDGF</td>
<td>platelet-derived growth factor</td>
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<td>PE</td>
<td>plasma exchange</td>
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<td>placental growth factor</td>
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<td>proteinase 3</td>
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<td>patient reported outcome measure</td>
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<td>percutaneous transluminal angioplasty</td>
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<td>PTU</td>
<td>propylthiouracil</td>
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<td>rheumatoid arthritis</td>
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<td>RANTES</td>
<td>regulated on activation, normal T cell expressed and secreted</td>
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<td>Rituximab for ANCA associated Vasculitis (Trial)</td>
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<td>rituximab</td>
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<td>RSD</td>
<td>reflex sympathetic dystrophy</td>
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<tr>
<td>RTX</td>
<td>rituximab</td>
</tr>
<tr>
<td>SAA</td>
<td>serum amyloid A protein</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
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<td>--------------</td>
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<tr>
<td>SAP</td>
<td>serum amyloid P component</td>
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<td>SAPS</td>
<td>secondary anti-phospholipid antibody syndrome</td>
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<td>Safety of Estrogen in Lupus Erythematosus National Assessment</td>
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<td>Short Form-36</td>
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<td>SLEDAI</td>
<td>Systemic Lupus Erythematosus Disease Activity Index</td>
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<td>Systemic Lupus International Collaborating Clinics/American College of Rheumatology</td>
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<td>spectrum emission computed tomography</td>
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<td>SRC</td>
<td>scleroderma renal crisis</td>
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<td>SS</td>
<td>Sjögren’s syndrome</td>
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<td>sulfasalazine</td>
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<td>scleroderma</td>
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<td>SUA</td>
<td>serum uric acid</td>
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<td>SVR</td>
<td>sustained virological response</td>
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<td>Syk</td>
<td>spleen tyrosine kinase</td>
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<td>TA</td>
<td>Takayasu arteritis</td>
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<td>TACI</td>
<td>transmembrane activator and calcium-modulator and cytoplphilin ligand interactor</td>
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<td>TBM</td>
<td>tubular basement membrane</td>
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<td>TCR</td>
<td>T cell receptor</td>
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<td>TCZ</td>
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<td>transforming growth factor</td>
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<td>TINU</td>
<td>tubulo-interstitial nephritis and uveitis syndrome</td>
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<td>TMA</td>
<td>thrombotic microangiopathy</td>
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<td>tumour necrosis factor</td>
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<td>thiopurine methyltransferase</td>
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<td>TRI</td>
<td>tubuloreticular inclusions</td>
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<td>TTP</td>
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<td>transthyretin</td>
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<td>Vasculitis Activity Index</td>
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<td>VDI</td>
<td>Vasculitis Damage Index</td>
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<td>VDRL</td>
<td>Venereal Disease Research Laboratory</td>
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<tr>
<td>VL</td>
<td>variable region</td>
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<td>VR</td>
<td>virological response</td>
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<td>vWF</td>
<td>von Willebrand factor</td>
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<td>Wegener’s granulomatosis</td>
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<td>World Health Organization</td>
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Chapter 1

Clinical presentation and assessment of disease activity in lupus nephritis

Venkat Reddy and David Isenberg

Introduction

Clinically evident lupus nephritis (LN) occurs in 35–75% of patients with systemic lupus erythematosus (SLE). The prevalence of renal involvement in patients presenting at around 50 years of age is about 60%, whereas about 80% of children have renal involvement during the course of their illness. LN usually occurs within 3 years after diagnosis of SLE. An adequate renal biopsy sample with immunofluorescence and electron microscopy is likely to show abnormalities in most patients with SLE.

In African-Caribbeans and African-Americans, LN occurs more frequently than in Caucasians, the disease tends to be more aggressive and has worse outcomes. Chinese patients might have up to 19 times higher risk of developing lupus than Caucasians. A higher prevalence has also been reported in Asians and Hispanics. Estimates of progression to renal failure vary from 10–15% in 1999, to just 4% in our own study of 401 patients followed for up to 25 years. Medical costs and resource utilization are substantially higher in patients with LN than those without. Early treatment may result in better outcomes in patients with LN.

Clinical manifestations

Patients with active LN often have features of active SLE such as a vasculitic rash, serositis, mouth ulcers, neurological features, alopecia, fever, fatigue and arthritis. LN rarely occurs in isolation or as a presenting feature.

Clinical presentations

In patients with LN, the most common finding is proteinuria (100%), followed by microscopic haematuria (80%), tubular abnormalities (60–80%), nephrotic syndrome (45–60%), hypertension (15–50%), granular casts (30%) and rapidly declining renal function (30%). However, LN may be ‘clinically silent’ with no urinary or biochemical abnormalities.
**Nephrotic syndrome**

A nephrotic syndrome occurs in 45–60% of patients with LN. The glomerular filtration rate (GFR) is usually not affected initially but a gradual reduction may be seen. Hypertension is common, particularly in patients with secondary antiphospholipid antibody syndrome (SAPS).

In a third of patients with LN, microscopic haematuria and non-nephrotic range proteinuria are seen, and GFR is usually not affected. These patients may remain in remission for a number of years.

In some patients, a rapid deterioration in renal function can occur. Hypertension is common and other features of active SLE might be present. ‘Nephritic flares’ with elevated creatinine are associated with worse outcomes. A nephritic flare with normal levels of serum creatinine increases the risk of renal impairment by 6.8 times, but when the flare is associated with elevated creatinine then the risk increases to 27 times. Acute renal failure secondary to pure LN is very rare. When this occurs, other causes of renal impairment such as hypovolaemia, urinary tract or systemic infection, nephrotoxic medications and renal vein thrombosis (uncommon) should also be considered.

**Assessment of disease activity**

During the course of LN, recurrent ‘nephritic flares’ may occur with resultant chronic damage. It is essential to distinguish active disease from chronic damage, to facilitate the appropriate use of immunosuppressive or biological therapies. Disease activity indices such as the British Isles Lupus Assessment Group (BILAG), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Systemic Lupus Activity Measure (SLAM) are validated and widely used. There is a high degree of correlation between all the three indices and they are sensitive to change. These indices have been used to rate response of both real and ‘paper’ patients.

**BILAG**

The BILAG index was developed to assess disease activity using the ‘intention to treat’ principle. Since its inception between 1984 and 1986, it has been revised on several occasions. The most recently updated version is the BILAG 2004.

In the latest version a comprehensive set of 98 items is assessed, aiming to ‘capture’ disease activity due to lupus, in nine organs or systems. The disease activity in each system is an assessment of activity over the previous month and the physician rates the activity as improving, the same, worse or new. Further, the results of key investigations including urine analysis, haematological indices and, if appropriate, cardio-pulmonary tests are also recorded.

A computerized British Lupus Integrated Program (BLIPS) is available to convert the clinical assessments to activity, which is categorized from A to E: Category A represents high disease activity (deemed likely to require more than 20 mg of prednisolone and or immunosuppressive drugs), Category B – moderate disease activity, Category C – mild disease activity, Category D – inactive disease in a previously active organ/system and Category E – no previous disease. The BILAG questionnaire requires the physician to complete a set of questions relating to (mostly) clinical features and
records them provided he/she believes that the clinical feature is due to SLE. A small number of laboratory results, for example the serum creatinine and haematology are added later. From this ‘raw’ data, either by hand or using computer software, a BILAG A–E score can be determined for each of the eight organ systems using the original BILAG or nine using the updated version. Physicians might at a glance infer whether there has been any ‘meaningful change’ in the disease activity for each organ system. Any changes to treatment are also recorded at every visit. The BLIPS system also contains the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index and it is possible to calculate the SLAM and SLEDAI global scores from the existing data. Further, the patient’s functional element is also considered using the validated instrument SF-36 Patient Health Questionnaire. The patients’ therapies and a full range of blood and other laboratory tests can also be recorded. Thus, the BLIPS system is a composite assessment of patients with SLE. The renal component of BILAG 2004 is shown in Table 1.1.1

In a collaborative nature Petri and colleagues attempted a comparison of the BILAG index and a broadly similar but unvalidated index (RIFLE, Responder Index For Lupus Erythematosus). The results were disappointing showing poor overall agreement, although problems with the methodology used may have been partly to blame. Another suggested renal activity and renal response index was proposed, which was found to have a reasonable degree of agreement with the BILAG index (overall percentage of 78%). The variables included were urine protein 0.5–1 g/day, urine protein 1–3 g/day, urine protein >3 g/day, urine red blood cell count 5–10/high-power field (hpf), urine red cell count >10/hpf, urine white blood cell count 5–10/hpf, urine white blood cell count >10/hpf, serum creatinine 1–1.5 mg/dl, serum creatinine >1.5 mg/dl, GFR 60–90 ml/minute/1.73m² and GFR <60 ml/minute/1.73m². Based on pre-defined criteria (specific changes in each renal parameter), the clinician is able to determine whether the individual patient has achieved a complete response, partial response, same/no change or worsening of the renal disease activity.21 The RIFLE index has been shown to have a good physician plurality rating.22

**SLICC/ACR index**

The SLICC/ACR index is a cumulative global damage index. It captures items of permanent change occurring after the diagnosis of SLE has been made from whatever cause. Often the cause is multifactorial, for example a lupus patient who develops a cataract and who has been on steroids, has a point with a cataract that has developed as a result of a combination of steroids and diabetes. Renal damage items recorded are: estimated GFR of <50%, proteinuria of >3.5 g/24 hours (each scoring 1 point) or end-stage renal disease (regardless of dialysis or transplantation, scores 3 points).23

**Biochemical markers of disease activity**

**Urinary markers**

In theory, the 24 hour urine protein-to-creatinine ratio (PCR) is more reliable than a spot urine PCR, in the assessment of LN. Serial measurements of PCR correlate with
### Table 1.1 Renal assessment: BILAG index 2004

#### Category A
Two or more of the following providing 1, 4 or 5 is included:

1. Deteriorating proteinuria (severe) defined as
   - urine dipstick increased by $\geq 2$ levels (used only if other methods of urine protein estimation not available); or
   - 24 hour urine protein $\geq 1$ g that has not decreased (improved) by $\geq 25\%$; or
   - urine protein:creatinine ratio $>100$ mg/mmol that has not decreased (improved) by $\geq 25\%$; or
   - urine albumin:creatinine ratio $>100$ mg/mmol that has not decreased (improved) by $\geq 25\%$

2. Accelerated hypertension

3. Deteriorating renal function (severe) defined as
   - plasma creatinine $>130$ μmol/l and having risen to $>130\%$ of previous value; or
   - GFR $<80$ ml/min per 1.73 m$^2$ and having fallen to $<67\%$ of previous value; or
   - GFR $<50$ ml/min per 1.73 m$^2$, and last time was $>50$ ml/min per 1.73 m$^2$ or was not measured

4. Active urinary sediment

5. Histological evidence of active nephritis within last 3 months

6. Nephrotic syndrome

#### Category B
One of the following:

7. One of the Category A features

8. Proteinuria (that has not fulfilled Category A criteria)
   - urine dipstick that has risen by 1 level to at least 2+ (used only if other methods of urine protein estimation not available); or
   - 24 hour urine protein $\geq 0.5$ g that has not decreased (improved) by $\geq 25\%$; or
   - urine protein:creatinine ratio $\geq 50$ mg/mmol that has not decreased (improved) by $\geq 25\%$; or
   - urine albumin:creatinine ratio $\geq 50$ mg/mmol that has not decreased (improved) by $\geq 25\%$

9. Plasma creatinine $>130$ μmol/l and having risen to $\geq 115\%$ but $\leq 130\%$ of previous value

#### Category C
One of the following:

10. Mild/Stable proteinuria defined as
    - urine dipstick $\geq 1+$ but has not fulfilled criteria for Category A & B (used only if other methods of urine protein estimation not available); or
    - 24 hour urine protein $>0.25$ g but has not fulfilled criteria for Category A & B; or
    - urine protein:creatinine ratio $>25$ mg/mmol but has not fulfilled criteria for Category A & B; or
    - urine albumin:creatinine ratio $>25$ mg/mmol but has not fulfilled criteria for Category A & B
disease activity. In patients with normal range proteinuria, the albumin-to-creatinine ratio may be more useful in predicting a renal flare. However, in practice obtaining a truly reliable 24 hour urine collection is fraught with difficulty. Patients often miss out samples and do not like travelling on public transport with large containers full of their own urine. There is, furthermore, very good correlation between spot urine PCR and the 24 hour protein over a wide range of measurement. Thus, the much greater ease of obtaining a ‘spot’ test means that this technique is now widely used. Urinary cellular casts might be a better predictor of renal relapse than increasing haematuria or decreasing serum third component of complement system (C3). Other markers under evaluation include: 1) serial urinary and serum neutrophil gelatinase-associated lipocalin levels, which might predict renal flare up to 3 months before a clinical flare is evident, 2) urinary lipocalin-2 levels, which are reported to be higher in patients with SLE nephritis when compared with SLE patients without nephritis and healthy controls, 3) urinary proteomic profile and 4) urinary FOXP3 mRNA, which correlates with active LN.

Serum markers
Defective clearance of apoptotic cells and autoreactive T cells results in persistent exposure of self-antigens (cellular components) resulting in autoimmunity. This mechanism may explain the finding of a number of autoantibodies described in association with lupus nephritis.

Autoantibodies
Anti-dsDNA antibodies (present in up to 90% of untreated patients with LN) and antibodies to anti-C1q (present in 80–100%) are often abnormal in patients with LN and in many cases their levels correlate with disease activity. Anti-Sm antibody is positive in up to 30% of black patients and often correlates with LN but does not necessarily indicate active disease. The combination of rising titres of anti-dsDNA with decreasing concentrations of C3, was found to correlate very well with active LN. However, this correlation is not seen in membranous nephropathy. Anti-endothelial cell antibodies

Table 1.1 (continued) Renal assessment: BILAG index 2004

| Category D | Previous involvement |
| Category E | No previous involvement |

Although albumin:creatinine ratio and protein:creatinine ratio are different, we use the same cutoff values for this index.

GFR, glomerular filtration rate.
correlate with proliferative nephritis. Anti-nucleosome antibodies may predict nephritic flare in patients with serologically active and clinically quiescent patients.

A prospective longitudinal study of new onset LN patients followed up for 2 years, showed that anti-nucleosome antibodies and anti-dsDNA antibodies correlated positively with urine PCR and negatively with serum albumin. There was no such correlation with anti-α-actinin antibodies.

A cross-sectional study of 33 patients with active lupus nephritis (BILAG disease activity index) showed that antibodies to heparan sulphate correlated with active nephritis. In this study, serial measurements of autoantibodies in eight patients with biopsy-proven lupus nephritis indicated that the levels of anti-dsDNA antibodies did not correlate with active nephritis in every patient. However, a higher proportion of patients with active LN, had anti-ssDNA, anti-dsDNA, anti-heparan sulphate, antihistone and anti-nucleosome antibodies than those without active LN. There was a high prevalence of anticardiolipin antibodies, anti-dsDNA and anti-C1q antibodies in patients with LN. There was no such association observed with anti-β₂-glycoprotein I (β₂-GPI).

Antiphospholipid syndrome nephropathy (APSN)

Renal involvement is seen in both primary antiphospholipid syndrome (APS) and secondary APS associated with SLE. Kidney involvement is more common in secondary antiphospholipid syndrome than in primary antiphospholipid syndrome (68% vs 30%) respectively. APSN is an independent risk factor for hypertension and can occur both independently and in association with LN. A greater correlation was seen with lupus anticoagulant than with antiphospholipid antibodies. Interestingly, arterial thromboses and foetal loss, but not venous thromboses were commonly associated with APSN.

Conclusions

Nephritis is very common in patients with SLE. Clinical manifestations and outcomes are highly variable. Ethnicity, age at presentation and the histological types are important independent prognostic factors. The varied clinical manifestations of LN are due to a combination of the pleomorphic histological manifestations, hypertension (frequent) and the immunosuppressive therapies. Early detection of the different patterns of the clinical manifestations would facilitate appropriate management without delay.

The BLIPS system is a composite means of assessing the disease activity in an individual organ/system. The BILAG, SLAM and SLEDAI are all validated indices of disease activity. Urine dipstick analysis for PCR remains the common, reliable monitoring method in practice. However, improvement in proteinuria may lag behind clinical remission in patients responding to treatment. Other urinary markers currently being evaluated are likely to be more useful in distinguishing responders to treatment early.

A combination of rising titres of anti-ds DNA antibodies, hypocomplementaemia is associated with a nephritic flare, but not in all patients. Anti-nucleosome antibodies are useful when predicting a flare. Renal biopsy remains the gold standard diagnostic
methodology and a repeat biopsy is indicated for non-responders. Active lesions and tubulo-interstitial nephritis are important prognostic indicators. Successful therapy might result in histological class switch. APS nephropathy might superimpose and warrants treatment with anticoagulation.

**Take home points**

1. There is renal involvement in 35–75% of patients with SLE.
2. Relatively few patients develop renal failure and failure of treatment compliance is often a major contributory factor.
3. Defining whether renal abnormalities are due to activity, damage or a combination of both is important in guiding treatment.
4. General activity indices such as the BILAG or SLEDAI scoring systems, together with more specific indicators (e.g. PCR and the presence of urinary red cells and casts) provide an optimal way of assessing disease activity in a patient with lupus nephritis.
5. Renal biopsy remains an essential ‘tool’ in determining the type of lupus involvement, the degree of activity and damage, and the outcome.

**References**

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest

   **A comprehensive overview of lupus nephritis including the clinical manifestations, aetiopathogenesis, illustrative immunohistological features and management of lupus nephritis.**

   *In this study group, renal disease was a major feature in both primary and secondary antiphospholipid syndrome, renal thrombosis leading to renal disease and hypertension.*


   *This article highlights the need to evaluate for subclinical renal disease in patients with SLE.*


*This study highlights the ethnic disparities in the context of SLE.*


*The findings from this study group suggest that several factors including the severity of kidney biopsy findings, contribute to the poor prognosis in Black patients.*


*This article highlights factors other than socio-economic, such as genetic and adherence to medications, that play a significant contribution to the outcome in the management of lupus nephritis.*


*The authors discuss the significance of cardiolipid antibody status in the context of lupus nephritis.*

Chapter 2

Lupus nephritis: Histopathology

David J. Cimbaluk and Melvin M. Schwartz

Introduction

The renal biopsy is critical in the management of systemic lupus erythematosus (SLE). It answers important questions concerning the current status and the long-term prognosis of the kidney and the patient with SLE by providing a direct assessment of renal involvement that is independent of the clinical findings and that cannot be accurately predicted on the basis of clinical manifestations.1 Because SLE can involve any renal compartment (glomeruli, tubulo-interstitium, blood vessels), the biopsy establishes the site of injury. In addition, there is a new classification of lupus nephritis developed by the International Society of Nephrology and the Renal Pathology Society (ISN/RPS)2 that allows assignment of lesion-specific therapy and prognostication.

The statistical problem imposed by the glomerular sample size is an important limitation of the renal biopsy. Because renal biopsies are usually performed for signs of glomerular involvement and because SLE glomerular pathology is characteristically focal (only a proportion of the glomeruli are involved), larger samples are more accurate in defining the presence and extent of glomerular involvement. For instance, if 10% of glomeruli are actually involved, there is a 35% probability that no abnormal glomeruli will be seen in a biopsy containing only 10 glomeruli. However, the probability of missing a focal lesion falls to 12% in a biopsy containing 20 glomeruli.3 The statistics imply that unless there is a diagnostic glomerular lesion, a biopsy with fewer than 10 glomeruli is insufficient for diagnosis.

This chapter has three goals: to describe the renal pathology of lupus nephritis and the classification of the glomerular lesions; to review the prognosis of the ISN/RPS classes of glomerular pathology; and to identify the critical questions that the renal biopsy answers.

Lupus nephritis

Glomerular pathology

The pathological features of SLE (Table 2.1) denote either ‘active lesions’ (potentially reversible acute inflammation) or ‘inactive lesions’ (irreversible scarring).
Hypercellularity

Proliferation of glomerular endothelial, mesangial and epithelial cells, and infiltration of leucocytes is the most frequent histological finding in lupus nephritis. Mesangial hypercellularity is a response to a variety of glomerular injuries and is usually accompanied by mesangial matrix expansion. Although it varies in intensity, isolated mesangial hypercellularity is associated with mild forms of lupus nephritis. Endocapillary hypercellularity comprises endothelial cell proliferation and leucocyte infiltration that occludes the glomerular capillary (Fig. 2.1). Endocapillary proliferation is an ‘active’ glomerular lesion, indicating a more serious form of glomerulonephritis (GN).

Crescents

Crescents (epithelial cell proliferation and leucocyte infiltration in Bowman’s space–extracapillary proliferation) (Fig. 2.2) are a feature of active lupus nephritis. The greater

**Table 2.1** Active and chronic glomerular lesions considered to reflect the presence or absence of activity in patients with SLE (data from\(^2\))

<table>
<thead>
<tr>
<th>Active glomerular lesions</th>
<th>Inactive glomerular lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocapillary hypercellularity</td>
<td>Glomerular sclerosis (segmental or global)</td>
</tr>
<tr>
<td>Karyorrhexis</td>
<td>Fibrous adhesions</td>
</tr>
<tr>
<td>Fibrinoid necrosis</td>
<td>Fibrous crescents</td>
</tr>
<tr>
<td>Rupture of glomerular basement membrane</td>
<td></td>
</tr>
<tr>
<td>Crescents, cellular or fibrocellular</td>
<td></td>
</tr>
<tr>
<td>Wire loops</td>
<td></td>
</tr>
<tr>
<td>Hyaline thrombi</td>
<td></td>
</tr>
</tbody>
</table>

**Fig. 2.1** Endocapillary proliferation. Glomerular hypercellularity in lupus nephritis is usually due to proliferation of cells normally found within the basement membrane (endothelial and mesangial cells) and infiltrating leucocytes (monocytes and neutrophils). In the figure the capillary lumens are occluded by the proliferating cells. Jones stain (methenamine silver periodic acid Schiff), ×165.
the proportion of glomerular involvement, the worse the prognosis, and when more than 50% are involved (crescentic glomerulonephritis), the renal prognosis is very poor. With evolution of the glomerular injury, there is progressive scarring of cellular crescents, forming fibrocellular and fibrous crescents.

**Karyorrhexis**

Karyorrhexis refers to degenerative and fragmented nuclei, resulting from necrosis or apoptosis.\(^2\) Karyorrhexis implies a destructive inflammatory lesion that is frequently associated with other histological signs of necrosis.

**Fibrinoid necrosis**

Fibrinoid is an extracellular inflammatory exudate (fibrin, serum proteins, immune aggregates and extracellular matrix proteins such as fibronectin) seen in areas of severe glomerular inflammation. Necrosis is a destructive inflammatory lesion that heals with scarring and is frequently associated with crescent formation. The histological diagnosis of necrosis is established by the triad of neutrophilic infiltrates with karyorrhexis, fibrin and ruptures (breaks) of the glomerular basement membrane (GBM).

**Wire loop**

Wire loops, a classic sign of active lupus nephritis,\(^4\) are segmental areas of refractile, eosinophilic, thickening of the GBM seen by light microscopy\(^4\) (Fig. 2.3). They correspond to massive capillary wall immune aggregates (fluorescence microscopy) and subendothelial electron-dense deposits, and to preserve their significance as a sign of severe GN, small subendothelial deposits seen by electron microscopy are not to be confused with wire loops.
Hyalin thrombi
Hyalin thrombi are acellular, eosinophilic, periodic acid-Schiff (PAS) positive masses, which occlude the glomerular capillary lumens. They are an infrequent finding in lupus nephritis, and they consist of immune reactants without significant amounts of fibrin.\textsuperscript{5-7}

Glomerular sclerosis
Global or segmental glomerular scars result from severe or prolonged glomerular damage in the course of ‘active’ glomerular lesions.

Immunofluorescence microscopy
In lupus nephritis, immune deposits can be detected in all renal compartments.\textsuperscript{1} Although glomerular patterns of immunofluorescence staining are highly variable (see below, ISN/RPS classes), some general features apply to all classes. Glomerular IgG is found almost universally with lesser amounts of IgM and IgA codeposited. ‘Full house’ staining refers to the presence of all three immunoglobulin classes. C3 is the most frequent complement component, followed by C1q.

Ultrastructural findings
Electron microscopy identifies the intraglomerular location of deposits. In addition, several features that are characteristic, but not diagnostic of SLE, are visible only with the electron microscope. These include tubular reticular structures in endothelial cells\textsuperscript{8} and organized electron-dense deposits (fingerprints).

The 2003 ISN/RPS classification of lupus nephritis
The ISN/RPS classification was proposed in 2003 by a consensus conference of renal pathologists, nephrologists and rheumatologists sponsored jointly by the International
THE 2003 ISN/RPS CLASSIFICATION OF LUPUS NEPHRITIS

Society of Nephrology and the Renal Pathology Society (Table 2.2). It is a modification of the previous, widely accepted World Health Organization (WHO) classification, and it intended to remedy perceived problems in the WHO classifications by standardizing definitions, eliminating ambiguities and improving interobserver agreement and reproducibility. The six classes of the ISN/RPS classification are summarized below.

ISN/RPS Class I: Minimal mesangial lupus nephritis

Class I is normal glomeruli by light microscopy with mesangial immune deposits by immunofluorescence and electron microscopy. This is the mildest form of lupus nephritis, and Class I patients have minimal clinical renal disease. The prognosis is no different from SLE patients without renal involvement. In previous WHO classifications, Class I included a ‘normal’ renal biopsy, but because it is contradictory to refer to a normal biopsy as a manifestation of disease, this category was eliminated.

ISN/RPS Class II: Mesangial proliferative lupus nephritis

The glomeruli in Class II may have any degree of mesangial hypercellularity and mesangial immune deposits. Any active or inactive lesion (Table 2.1) or significant subendothelial deposits (wire loops) disqualify the biopsy from this class. Most Class II patients have asymptomatic urinary abnormalities. Although there is proteinuria in half, nephrotic syndrome and renal insufficiency are uncommon. The combination of the nephrotic syndrome and diffuse foot process effacement seen by electron microscopy in biopsies from ISN/RPS classes I or II is consistent with a non-immunoglobulin mediated lupus ‘podocytopathy’. The prognosis of ISN/RPS Class II is good.

ISN/RPS Class III: Focal lupus nephritis

Class III requires any active or chronic glomerular lesion (Table 2.1), involving less than 50% of all glomeruli (Fig. 2.4). In general, the glomerular pathology of Class III involves only a portion of the glomerulus (segmental) and it is often necrotic. Because Class III lesions characteristically occur without significant subendothelial deposits (wire loops), it has been postulated that these vasculitis-like lesions are not caused by the immune complex mechanisms usually attributed to SLE. However, this point is controversial, and many pathologists believe that focal GN (Class III) and diffuse GN (Class IV) have the same pathogenesis, with diffuse GN being a more advanced, progressive form of the disease. In any case, qualitatively similar glomerular lesions are classified in Class IV if the pathology is seen in ≥50% of glomeruli (see below, Diffuse lupus nephritis). In determining the percentage of glomeruli affected, both active and chronic lesions are counted.

Class III patients often have clinical evidence of renal involvement, but the variable glomerular pathology (1–50% focal involvement) is reflected by a spectrum of presentations from isolated haematuria and/or proteinuria to nephritic or nephrotic syndrome. Although the natural history (untreated) of patients with ISN/RPS Class III lupus GN is unknown, these lesions are capable of progression, especially when they involve a higher proportion of the glomeruli (25–50%). However, the prognosis of treated Class III patients approaches the survival of SLE patients.
<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td><strong>Minimal mesangial lupus nephritis</strong></td>
</tr>
<tr>
<td></td>
<td>Normal glomeruli by light microscopy, but mesangial immune deposits</td>
</tr>
<tr>
<td></td>
<td>by immunofluorescence</td>
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<tr>
<td>II</td>
<td><strong>Mesangial proliferative lupus nephritis</strong></td>
</tr>
<tr>
<td></td>
<td>Purely mesangial hypercellularity of any degree or mesangial matrix</td>
</tr>
<tr>
<td></td>
<td>expansion by light microscopy, with mesangial immune deposits</td>
</tr>
<tr>
<td>III</td>
<td><strong>Focal lupus nephritis</strong></td>
</tr>
<tr>
<td></td>
<td>Active or inactive focal, segmental or global endo- or extracapillary</td>
</tr>
<tr>
<td></td>
<td>glomerulonephritis involving &lt;50% of all glomeruli, typically with focal</td>
</tr>
<tr>
<td></td>
<td>subendothelial immune deposits</td>
</tr>
<tr>
<td>III (A)</td>
<td>Active lesions: focal proliferative lupus nephritis</td>
</tr>
<tr>
<td>III (A/C)</td>
<td>Active and chronic lesions: focal proliferative and sclerosing lupus</td>
</tr>
<tr>
<td></td>
<td>nephritis</td>
</tr>
<tr>
<td>III (C)</td>
<td>Chronic inactive lesions with glomerular scars: focal sclerosing lupus</td>
</tr>
<tr>
<td></td>
<td>nephritis</td>
</tr>
<tr>
<td>IV</td>
<td><strong>Diffuse lupus nephritis</strong></td>
</tr>
<tr>
<td></td>
<td>Active or inactive diffuse, segmental or global endo- or extracapillary</td>
</tr>
<tr>
<td></td>
<td>glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse</td>
</tr>
<tr>
<td></td>
<td>subendothelial immune deposits</td>
</tr>
<tr>
<td></td>
<td>This class is divided into diffuse segmental (IV-S) lupus nephritis when</td>
</tr>
<tr>
<td></td>
<td>≥50% of the involved glomeruli have segmental lesions, and diffuse global</td>
</tr>
<tr>
<td></td>
<td>(IV-G) lupus nephritis when ≥50% of the involved glomeruli have global</td>
</tr>
<tr>
<td></td>
<td>lesions</td>
</tr>
<tr>
<td></td>
<td>Segmental is defined as a glomerular lesion that involves less than half</td>
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<tr>
<td></td>
<td>of the glomerular tuft</td>
</tr>
<tr>
<td>IV-S (A)</td>
<td>Active lesions: diffuse segmental proliferative lupus nephritis</td>
</tr>
<tr>
<td>IV-G (A)</td>
<td>Active lesions: diffuse global proliferative lupus nephritis</td>
</tr>
<tr>
<td>IV-S (A/C)</td>
<td>Active and chronic lesions: diffuse segmental proliferative and sclerosing</td>
</tr>
<tr>
<td></td>
<td>lupus nephritis</td>
</tr>
<tr>
<td>IV-G (A/C)</td>
<td>Active and chronic lesions: diffuse global proliferative and sclerosing</td>
</tr>
<tr>
<td></td>
<td>lupus nephritis</td>
</tr>
<tr>
<td>IV-S (C)</td>
<td>Chronic inactive lesions with scars: diffuse segmental sclerosing lupus</td>
</tr>
<tr>
<td></td>
<td>nephritis</td>
</tr>
<tr>
<td>IV-G (C)</td>
<td>Chronic inactive lesions with scars: diffuse global sclerosing lupus</td>
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<tr>
<td></td>
<td>nephritis</td>
</tr>
<tr>
<td>V</td>
<td><strong>Membranous lupus nephritis</strong></td>
</tr>
<tr>
<td></td>
<td>Global or segmental subepithelial immune deposits or their morphologic</td>
</tr>
<tr>
<td></td>
<td>sequelae by light microscopy by immunofluorescence or electron microscopy</td>
</tr>
<tr>
<td>VI</td>
<td><strong>Advanced sclerotic lupus nephritis</strong></td>
</tr>
<tr>
<td></td>
<td>≥90% of glomeruli globally sclerosed without residual activity</td>
</tr>
</tbody>
</table>

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without renal involvement (82% at 5 years without death or renal failure).\textsuperscript{26} Although Class III lupus nephritis may form glomerular scars and transform to diffuse lupus nephritis, treatment appears to abrogate these adverse outcomes. It should be noted that if these patients are included in therapeutic trials,\textsuperscript{29,30} their responsiveness may improve overall outcome without affecting the outcome of patients with more widespread glomerular involvement (see below, Diffuse lupus nephritis).

**ISN/RPS Class IV: Diffuse lupus nephritis**

Class IV includes any of the active and/or chronic glomerular lesions (Table 2.1), involving $\geq 50\%$ of glomeruli, and it has the worst prognosis of all the forms of lupus GN.\textsuperscript{26,27,31} The glomeruli contain large amounts of immunoglobulin and complement in the mesangium and capillary walls.

Class IV is subdivided into diffuse segmental lupus nephritis (Class IV-S) when $>50\%$ of the involved glomeruli have segmental lesions (pathology involves $<50\%$ of the tuft), and diffuse global lupus nephritis (Class IV-G) (Fig. 2.5) when $>50\%$ of the involved glomeruli have global lesions (pathology involves $>50\%$ of the tuft). This division is the most controversial aspect of the ISN/RPS 2003 classification. It was based on studies that used a broader definition of segmental GN\textsuperscript{23,25} and found that patients with segmental lupus GN involving more than 50% of the glomeruli have a worse outcome than diffuse global lupus GN.\textsuperscript{23} Three recent retrospective studies, using the ISN/RPS definitions, failed to show a worse outcome in IV-S vs IV-G.\textsuperscript{24,32,33} The different definitions of segmental and global SLE GN appear to be responsible for these divergent results.\textsuperscript{25}

Class IV patients usually have evidence of active systemic disease, and renal disease frequently dominates the clinical picture.\textsuperscript{13,14,16,19,27,34} Despite the overall improved survival for SLE patients,\textsuperscript{26,35} Class IV patients continue to have a poor prognosis.
LUPUS NEPHRITIS: HISTOPATHOLOGY

Despite optimal treatment, although heterogeneous morphologically, Class IV patients have similar clinical presentations, and 40% have an adverse outcome within 5 years of biopsy. The poor prognosis of patients with Class IV lupus nephritis relative to patients with less widely distributed classes of lupus nephritis, makes it imperative to recognize these quantitative differences in the extent of glomerular pathology among patients, and in evaluating therapeutic trials it is critical to note the proportion of Class IV patients because this aspect of study design will directly affect outcome.

ISN/RPS Class V: Membranous lupus nephritis

Class V has thickened basement membranes, but the Jones’ stain (methenamine silver periodic acid Schiff) is required to demonstrate the characteristic spikes, holes and thickening of membranous transformation. The sine qua non of Class V is diffuse, granular, immune aggregates and subepithelial and intramembranous electron-dense deposits. The granular deposits occur with or without mesangial deposits. Subepithelial granular deposits may also be seen in Class IV, but they are segmental and involve a smaller proportion of the capillaries. In contrast to the 1982 and 1995 WHO classifications, focal or diffuse proliferative GN accompanying MGN are diagnosed and classified separately (i.e. Class V + Class III or Class V + Class IV). Class V patients, uncomplicated by Class III or Class IV GN, have a clinical course and prognosis similar to patients with idiopathic MGN. They usually have proteinuria or the nephrotic syndrome, limited evidence of nephritis and renal insufficiency, and mild serological abnormalities.

ISN/RPS Class VI: Advanced sclerotic lupus nephritis

Glomerular scarring may follow active GN, and when scarring involves >90% of the glomeruli with no evidence of activity, the biopsy is classified as ‘advanced sclerosing lupus nephritis’.

Fig. 2.5 Diffuse global glomerulonephritis (ISN/RPS Class IV-G). This example of lupus nephritis has endocapillary proliferation occluding virtually all the glomerular capillaries (global). Similar changes were present in all the glomeruli in the biopsy (diffuse). Haematoxylin and eosin stain, ×158.
The 2003 ISN/RPS classification is widely utilized in the classification of lupus nephritis because of a number of logical changes that have made it easier to use and understand than its predecessors. These include elimination of the normal category (previously WHO class I), removal of the subclasses of lupus nephritis class V, use of simple mnemonics (A) and (C) to designate active and chronic lesions, and stricter definitions for all lesions and classes. Two studies have found a higher level of interobserver reproducibility with the ISN/RPS 2003 classification compared to the 1995 WHO classification that was attributed to clearer distinctions between classes, and this is considered a major achievement of the classification. However, the classification has been criticized because it is a morphological classification that does not take into account the varied pathogenetic mechanisms that may be active in lupus GN, and because it is a classification of SLE GN to the exclusion of the tubulo-interstitial and vascular pathologies that contribute to the spectrum of SLE renal pathology.

The definitions that are used to separate Class III from Class IV and Class IV-S from IV-G have also been criticized. The rules that govern sampling predict the 50% cutoff that distinguishes between classes III and IV is subject to sampling errors, implying that significant misclassifications will occur by chance. Thus, the precision of the definitions in the ISN/RPS classification do not ensure that the biopsy diagnosis will be a true representation of the pathology in the kidney. Additionally, separating diffuse GN (Class IV) into IV-S and IV-G is a complicated process: the portion of involved glomerular surface area has to be determined for each glomerulus, and then, the biopsy is assigned to IV-S or IV-G if a majority of the glomeruli have <50% or >50% involvement respectively. Qualitatively similar segmental lesions can involve < and >50% of the glomerular surface area, and because the ISN/RPS classification includes
segmental lesions with >50% glomerular surface area involvement in IV-G, it improves the prognosis of the ISN/RPS IV-S while worsening the prognosis of ISN/RPS IV-G. There is evidence that the pathogeneses of diffuse segmental lupus GN and diffuse global lupus GN are different, and it is important to understand that because the ISN/RPS classification obscures these differences, it removes important informational content from the renal biopsy. The implications of the ISN/RPS definitions for diagnostic accuracy, pathogenesis and prognosis have been reviewed in detail.25,47

**Tubulo-interstitial pathology**

Disease of the tubules and interstitium, including acute interstitial inflammation and oedema and tubular atrophy and interstitial fibrosis, are seen, and they are most common in Class IV lupus nephritis.1 Immunoglobulin deposits are seen in the interstitium, tubular basement membranes and in the walls of small renal blood vessels in up to 50% of biopsies, and they may play a pathogenetic role.48

**Vascular pathology**

Vascular lesions are common in renal biopsies from SLE patients and include uncomplicated vascular immune deposits, non-inflammatory necrotizing vasculopathy, thrombotic vasculopathy (Fig. 2.7), true inflammatory vasculitis and non-specific arteriosclerosis.1 Renal vascular lesions are associated with a high rate of progression to renal failure (the 5- and 10-year renal survival rates are 74.3% and 58.0%, respectively, for patients with renal vascular lesions, compared with 89.6% and 85.9% for those without renal vascular lesions).49

*Fig. 2.7* Glomerular thrombus. There is a large thrombus (asterisk) near the glomerular hilum. Thrombotic lesions can be seen in lupus patients with severe glomerulonephritis, the anticoagulant/anti-phospholipid syndrome, haemolytic uremic syndrome and TTP. Periodic acid Schiff stain, ×226.
Histological indices of renal pathology in SLE

Pathological indices, derived from semi-quantitative scoring of the histological signs of activity and inactivity (Table 2.1), have been proposed as better prognostic and therapeutic guides than the WHO classification,\textsuperscript{10,11} and the National Institutes of Health\textsuperscript{50} activity (AI) and chronicity (CI) indices are the most popular examples of this approach. The CI has been used to predict outcome\textsuperscript{50,51} and assess therapy.\textsuperscript{52} However, the generation and interpretation of the indices has been criticized.\textsuperscript{53}

Because numerous studies have failed to show a relation between the AI and outcome, its role as a therapeutic or prognostic guide appears to be unwarranted. When methodological problems are combined with a critique of the interpretation and implications of the CI, its validity as a therapeutic guide is also compromised. However, as a summary of the active (potentially responsive) and chronic (irreversible) lesions of lupus nephritis, the numerical score(s) of the indices may be used to help the pathologist communicate the character of the renal pathology to the clinician.

Transformations

Lupus nephritis is not a static entity, and the ability to transform from one class to another was documented between all classes in the previous WHO classification.\textsuperscript{19} Transformations to diffuse lupus nephritis (ISN/RPS Class IV) from the lesser forms of lupus nephritis are obviously the most significant. Transformation and glomerular scarring can lead to complex lesions, but they can be readily classified by the ISN/RPS classification.

Take home points

1. Is renal dysfunction caused by lupus or a non-SLE renal lesion?
   Renal insufficiency in SLE may be caused by SLE-related glomerular pathology, tubulo-interstitial or vascular pathology, or non-SLE pathogenic mechanisms such as prerenal hemodynamic factors or a drug-related tubulo-interstitial nephritis. In general, if the biopsy shows active lupus nephritis (Class III or IV), renal insufficiency should be attributed to the glomerular disease. If the biopsy shows one of the less inflammatory forms or glomerular involvement (Class I, II, or V), and there is acute tubulo-interstitial nephritis, a non-lupus aetiology should be excluded, clinically. The presence of both lupus GN and tubulo-interstitial damage requires treatment of the glomerular lesion and removal of potentially damaging drugs from the therapeutic regimen.

2. How severe is the glomerular pathology?
   The renal biopsy documents the presence and distribution of pathology among the glomeruli. Using these observations, the pathologist makes a diagnosis based upon the ISN/RPS classification. The prognosis (and severity) of the lesion is implicit in the class of the glomerular pathology.

3. Is the pathology reversible?
   Whether the pathology seen on renal biopsy is reversible depends on the relative contribution of lesions that can be expected to heal with and without scarring.
By its nature, lupus nephritis can heal with scarring, and a glomerular scar implies a loss of function. Although the extent of glomerular scarring does not correlate well with function, the associated tubular atrophy and interstitial fibrosis directly correlate with the creatinine clearance. Thus, the pathology indicates reversibility of the lesion by describing the nature and the extent of glomerular inflammation (potentially reversible in the absence of necrosis) and the extent of glomerular scarring, interstitial fibrosis and tubular atrophy (irreversible lesions).

4. How should the patient be treated?

The renal pathology makes a major contribution to the answer of this critical question. Once it has been determined that the patient has lupus nephritis, the biopsy is placed into one of the ISN/RPS classes. The glomerular pathology of Class I and II lesions receives limited treatment in the absence of systemic disease activity. The lesion-specific treatment of proliferative (Classes III and IV) and membranous (Class V) forms of lupus nephritis has been recently reviewed. When renal insufficiency results from extensive, irreversible lesions (ISN/RPS Class VI), the renal biopsy may be used to support a decision not to treat.

References

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest


*Classic textbook on the renal pathology of lupus nephritis.*


*Definitions and applications of the ISN/RPS Classification of lupus nephritis.*


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   *Definition of severe lupus nephritis and a critique of the ISN/RPS distinction between diffuse segmental (IV-S) and diffuse global (IV-G) lupus glomerulonephritis.*
   *Current review of the treatment for severe lupus nephritis.*
   *Review of the role of mycophenolate mofetil in treating lupus nephritis.*
Chapter 3

Lupus nephritis: Complement in lupus

Michael G. Robson

Introduction

Complement is a system of proteins with activities that include the recruitment of inflammatory cells, cellular activation, cell lysis, antimicrobial defence, clearance of immune complexes and amplification of the humoral immune response. The complement system will be briefly summarized, but for a detailed overview the reader is referred to a recent review such as Dunkelberger and Song (2010). There are three pathways of activation of complement. The classical pathway is activated by immune complexes, initiated by the binding of C1q to the Fc portion of immunoglobulin. The alternative pathway is activated by C3 either spontaneously, in the fluid phase or by ‘activator’ surfaces on microorganisms or damaged cells lacking control mechanisms expressed on normal host tissues. The mannose-binding lectin (MBL) pathway is initiated by MBL and its associated mannose binding serine proteases MASP1, MASP2 and MASP3. These have homology with C1q and C1r/s respectively. MBL binds to carbohydrate residues on bacteria, and activates C4 by a pathway analogous to the classical pathway. The cleavage of C3 is the central event in complement activation by all three pathways. This generates C3b and C3a, as well as the formation of the C5 convertases, allowing terminal pathway activation. A simplified diagram of the complement system is shown in Fig. 3.1. The complement system is tightly regulated by a range of control proteins. Although there is evidence that immune complexes can activate the alternative pathway of complement in some situations, they initiate the classical pathway far more readily. Classical pathway activation is a feature of systemic lupus erythematosus (SLE) because immune complexes containing autoantibodies and nuclear components cause much of the pathogenesis of this disease. This classical pathway activation is reflected in the fact that C1q, C4 and C3 are depleted from serum, and deposited in the tissues.

This chapter is divided into three parts. First, the serological abnormalities of the complement system that are seen in patients with lupus will be described, with a discussion of the aetiology and clinical utility of these findings. Second, the localization of complement components in tissue samples of patients with lupus using immunohistochemical or immunofluorescent techniques will be reviewed, followed by some comments on the evidence that this complement activation contributes to tissue injury. The third section discusses the association of homozygous genetic deficiencies
of complement proteins with SLE that is seen in a small minority of patients. This is followed by an account of the theories that may explain this link.

**Serological abnormalities of the complement system**

There are two categories of serological abnormalities of complement that are commonly seen in patients with lupus. These are hypocomplementaemia due to activation and consumption of complement components, and autoantibodies to complement proteins. This section will discuss these in turn. Primary genetic deficiency of classical pathway components, although strongly associated with lupus, is far less common than acquired hypocomplementaemia, and is discussed in the third part of this chapter.
Hypocomplementaemia

There are many studies showing that when a population of patients with active lupus is compared with a population of patients with inactive disease, hypocomplementaemia correlates with disease activity. The most frequently measured parameters are C3, C4 and total haemolytic activity (CH50) and these have all been shown to correlate with disease activity. There are two main classes of acquired hypocomplementaemia. The most profound is that associated with the presence of anti-C1q autoantibodies and several studies have documented an association between anti-C1q antibody levels and hypocomplementaemia.2,3 The mechanism of this is not fully understood. The best hypothesis is that anti-C1q antibodies may fix to immune complexes and cells that have bound C1q and this amplifies the activation of the classical pathway leading to C4, C2 and, to a lesser extent, C3 activation and consumption. As we shall learn below, the presence of anti-C1q autoantibodies is strongly correlated with active disease in SLE. Disease activity in the absence of anti-C1q autoantibodies is also associated with complement activation and consumption in tissues. High titres of anti-DNA antibodies are often found in this situation and hypocomplementaemia tends to be less severe than that which accompanies the presence of anti-C1q antibodies.

The concentration of any protein in the blood is related to its synthetic and catabolic rates. In steady state, these are in equilibrium. In the case of the complement system and SLE, there are a series of very complex interactions in both synthesis and catabolism, which conspire to complicate the clinical interpretations of assays of complement levels in serum. As discussed above, the catabolism of complement proteins is generally increased by SLE disease activity. However, the synthetic rate may be decreased, normal or increased in SLE. This variation in synthetic rate in the context of increased catabolism serves to decrease the correlation of hypocomplementaemia with disease activity in lupus. A further factor that limits the clinical usefulness of complement measurements, especially in the case of C4, is the wide variation in the normal range. Two closely linked genes C4A and C4B, each of which shows a high degree of genetic polymorphism, encode C4. Included in this polymorphism are null alleles at the C4A and C4B loci, which are very common. Up to 40% of people of Western European origin express 1 or 2 null C4 alleles. What this means in effect is that the normal range of C4 levels is wide, encompassing subjects with two, three or four expressed C4 alleles.

Autoantibodies to complement proteins

In 1988, IgG autoantibodies to C1q (C1qAb) were isolated from five patients with SLE.4 The significance of these antibodies, in either the clinical monitoring or the pathogenesis of lupus has been the subject of much subsequent work. A significant correlation was found between C1qAb titres and particular clinical features including nephritis, dermatitis and hypocomplementaemia.2,3 Antibodies to C1q are not specific for SLE, and are found in a range of autoimmune diseases including severe rheumatoid arthritis, hypocomplementaemic urticarial vasculitis and mixed connective tissue disease.5 They have also been described in non-lupus types of glomerulonephritis, in particular mesangiocapillary glomerulonephritis, and in association with infections such as HIV and hepatitis C.
The mechanism by which C1qAb may exacerbate SLE has not been fully elucidated. Anti-C1q antibodies, binding to immune complexes that have fixed C1q, may amplify and increase the size of immune complexes. The association of C1qAb with hypocomplementaemia, discussed above, also supports the idea that C1qAb augments immune complex formation leading to complement activation. Using a murine model of glomerulonephritis, convincing evidence was obtained that monoclonal anti-C1q antibodies were not themselves pathogenic but could exacerbate immune complex-mediated glomerular disease.

Clinical utility of complement assays and anti-C1q antibody levels

As we have suggested above, caution must be exercised when using the results of complement assays to guide clinical decisions, despite the association of hypocomplementaemia with disease activity. Several studies have examined the utility of these measurements in the management of individual patients. One study included 99 patients and concluded that a normal C4 and DNA binding was rare with active disease, but that C4 could be low and DNA binding high with either active or inactive disease. In another study, C3, C4, CH50 and immune complexes were assayed in 33 patients, and none of these measured variables were found to show sufficient specificity or sensitivity to be useful measures of disease activity. However, specific complement assays may be identified as being useful in individual patients. In 11 of the 33 patients in the above study, a significant correlation was found between clinical disease activity and one or more of the measured serological parameters. Longitudinal measurements of complement activity are of more value in assessing changes in disease activity in SLE, although again are only useful in some patients. Serum complement and immune complex levels were studied in 27 patients through a cycle of disease exacerbation and remission. Exacerbations were divided, according to the nature of the clinical features into renal, extrarenal, or combined renal and extrarenal types. Measurements of C4 were most useful in the group with renal exacerbations. However, they were not so useful in the group with combined renal and extrarenal flares among which C4 was persistently low in virtually all patients.

A number of studies have emphasized the correlation of anti-C1q antibodies with active lupus nephritis. In one retrospective study, 14 of 24 anti-C1q antibody-positive patients had active lupus nephritis, and none of the 24 anti-C1q antibody-negative patients developed lupus nephritis, suggesting that a negative test may virtually exclude the presence of lupus nephritis. However, this precise negative predictive value has not been confirmed in all studies, and evaluation of 77 patients with active lupus nephritis found that 65% had anti-C1q antibodies. Thirty-three out of 83 patients without evidence of nephritis were also anti-C1q antibody positive, nine of whom went on to develop nephritis, suggesting that this group needs careful monitoring. Longitudinal studies have suggested that increasing levels of C1q antibodies may predict flares of nephritis by several months.

The above discussion has shown that measurement of C3, C4 and anti-C1q antibodies could all potentially be of use in guiding clinical decisions in patients with lupus,
providing that the limitations illustrated by these studies are appreciated. One of the largest studies published prospectively monitored these three markers, in addition to anti-dsDNA antibodies, in 228 patients with lupus nephritis. None of these four parameters had a good positive predictive ability, ranging from 28% to 38%. The negative predictive ability of all four tests was good at 91–94%. Although anti-C1q antibodies came top at 94%, there was little to choose between these assays. The best model for renal flare prediction came from combining C3, C4 and anti-C1q antibodies.

Complement deposition in the tissues
The first report of C3 deposition in glomerular lesions of lupus nephritis was in 1961. Since then, the presence of glomerular immune deposits of IgG, IgM, IgA, C3, C4 and C1q has become known as a characteristic feature of lupus nephritis. Immunoglobulin and C3 deposits are also found at the dermo-epidermal junction of diseased skin in most cases. Components of the membrane attack complex of complement have also been detected at the dermo-epidermal junction of lesional skin, and in glomeruli, of patients with lupus. The presence of complement components at sites of tissue inflammation and antibody deposits, as well as the acquired hyocomplementaemia, discussed above, suggests that complement plays a role in the effector arm of inflammatory injury in lupus.

The presence of complement components in tissue samples is not proof that they are mediating disease, and evidence questioning a major role for complement as an inflammatory mediator in SLE comes from animal models. C1q-deficient mice develop spontaneous lupus-like disease with anti-nuclear antibodies (ANA) production and glomerulonephritis. This parallels the development of lupus in C1q-deficient humans as discussed in the next section. Deposits of C3 were detected in glomeruli, which were compatible with complement alternative pathway activation by immune deposits within glomeruli. C1q-deficient mice were bred with mice lacking factor B and C2, unable to activate either the alternative or classical pathways of complement. These mice, with triple deficiency of C1q, C2 and factor B, developed spontaneous autoantibody production and glomerulonephritis. Analysis of renal tissue showed the presence of inflammatory glomerulonephritis with deposits of IgG and an absence of C3. Data in the MRLlpr lupus-prone mouse, rendered C3-deficient, has confirmed that complement activation is not required. These data show that complement activation is not necessary in order to develop lupus-type glomerulonephritis. There are, however, data that suggest complement can play a proinflammatory role in lupus. Decay accelerating factor (DAF) protects autologous cells from complement-mediated attack, and MRLlpr mice deficient in DAF have accelerated disease. In addition, treatment of lupus-prone mice with antibodies to C5 was shown to ameliorate disease. In keeping with this, more recent data has shown that the C5a receptor can stimulate disease through T cell-mediated effects. In contrast, the C3a receptor appears to promote a degree of protection, although the mechanism is not clear.

The other major pathway of immune complex-mediated inflammation, in addition to the complement system, is that mediated by leukocyte receptors for the Fc portion of IgG. Data from mice with gene-targeted mutations in Fc receptors illustrate that the major pathway for the transduction of immune complex-mediated glomerular inflammation in murine lupus, is by ligation of Fc receptors on leucocytes.
the evidence suggests that Fc receptors are necessary for the development of lupus nephritis. However, the situation regarding complement is complex, and there are data both for and against a proinflammatory role for complement.

**Genetic deficiency of classical pathway proteins as a cause of lupus**

The strongest genetic susceptibility to lupus is seen in patients with homozygous deficiencies of classical pathway complement proteins. I will first describe the epidemiology and clinical features of this association and then outline some theories that may explain this link.

**Epidemiology and clinical features**

There is a hierarchy of susceptibility to the development of SLE, and severity of disease according to the position of the deficient complement protein in the activation sequence of the classical pathway. The most severe and highly prevalent lupus is associated with a deficiency of C1q, C1r, C1s or C4. The frequency of lupus in C1 complex or C4 deficiency is greater than 80%. In the case of C2 deficiency, the frequency of lupus has probably been overestimated due to ascertainment artefact. There is likely to be a bias towards publishing C2-deficient subjects with SLE and not the occurrence of healthy C2-deficient individuals. Calculations based on the frequency of C2 deficiency among cohorts of patients with lupus, and the estimated frequency of C2 deficiency in the general population, suggest that around 10% of C2-deficient patients develop lupus. A genetic deficiency of complement as a cause of lupus may be missed easily if no functional assay of the complement cascade, such as a CH50 estimation, is performed. Clinical pointers to a hereditary complement deficiency are early onset of disease, the presence of disease in siblings and parental consanguinity. Persistently normal or elevated antigenic measurements in the face of active disease should also prompt measurement of the CH50. Patients with classical pathway deficiencies also suffer from recurrent pyogenic infections. In the case of C3 deficiency, pyogenic infections are the major clinical feature, and lupus is uncommon, being recorded in only three out of 23 cases.

In addition to these patients with complete genetic deficiencies of complement components, a question arises regarding the effect of partial deficiencies or polymorphisms. Data on the frequency of SLE in patients with partial C4 deficiency have been conflicting. Although lupus is not increased in people heterozygous for C1q deficiency, polymorphisms leading to lower C1q levels have been linked to both cutaneous and systemic lupus. There have been several studies assessing the role of polymorphisms in MBL in lupus (reviewed in). The data from these have been conflicting, due in part to small patient numbers. A complement receptor CR2 haplotype has also been found to be linked with lupus.

The cause of lupus in genetic deficiency of classical components of the complement pathway has not been established with certainty but may be a result of abnormal clearance of immune complexes and/or apoptotic cells or to a breakdown in immune tolerance mechanisms. We have discussed earlier the acquired hypocomplementaemia that commonly accompanies active disease. The mechanisms that explain how a genetic
complement deficiency leads to lupus may also serve to exacerbate disease in the presence of a secondary hypocomplementaemia.

**Clearance of immune complexes and apoptotic cells**

The complement system plays an important role in the processing of immune complexes. Data from experiments *in vitro* suggest that both the classical and the alternative pathway play a role in maintaining immune complexes in the soluble state.\(^3^2\) In addition, complexes that have fixed complement may bind to the erythrocyte complement receptor CR1, the ligands for which are C3b, iC3b and C4b. Red cell-bound complexes are then transported primarily to the spleen where they are taken up by macrophages. Patients with lupus have been found to have reduced numbers of red cell CR1. Most evidence favours this being an acquired deficiency rather than a primary genetic abnormality.\(^3^3\) This may be considered a further manifestation of the acquired hypocomplementaemia that occurs in lupus. As complement plays a role both in maintaining immune complexes in solution and in transporting them to the spleen where they may be safely disposed of, complement deficiency (primary or acquired) may be expected to augment immune complex deposition in tissues. In keeping with this hypothesis, defective clearance of radiolabelled immune complexes has been demonstrated in patients with SLE.\(^3^4\)

Complement plays a role in the clearance of apoptotic cells in addition to its activity in the safe removal of immune complexes. The presence of C1q has been demonstrated on the surface of apoptotic cells.\(^3^5\) In addition, complement deficiency reduces the clearance of apoptotic cells both *in vitro* and *in vivo* in a murine model.\(^3^6\) C1q-deficient mice have an excess of apoptotic cells in their glomeruli, suggesting that defective clearance of apoptotic cells may play a role in the generation of autoimmunity in these mice.\(^1^9\) How might an excess of apoptotic cells lead to the development of autoimmunity? Apoptotic cells have received interest as a potential source of autoantigens. Observations that support this possibility include the presence of nuclear antigens on the surface of apoptotic cells.\(^3^7\) Immunizing mice with apoptotic cells confirmed the immunogenicity of the nuclear antigens present on apoptotic cells. This resulted in the production of anti-dsDNA, anticardiolipin antibodies and glomerular IgG deposition.\(^3^8\)

**Complement deficiency and loss of tolerance**

In addition to effects on clearance of immune complexes or apoptotic cells, complement deficiency may cause lupus by promoting a loss of tolerance to self-antigens, through effects on lymphocytes or antigen-presenting cells. Tolerance to a transgenically expressed protein has been shown to depend on C4 (but not C3) and complement receptors CR1/2 specifically on B cells.\(^3^9\) Supporting a role for CR1/2 in lupus, this paper also showed that CR1/2- and C4-deficient mice were predisposed to lupus-like autoimmunity.

Although I have discussed above how complement deficiency may increase the availability of autoantigens and promote lupus, these antigens have to be presented by mature antigen-presenting cells. In this regard, a recent paper has added a new dimension to the mechanisms by which C1q deficiency may promote lupus. A large body of data supports a role for interferon alpha, which promotes dendritic cell activation, in
the pathogenesis of lupus, and it was shown that C1q can inhibit interferon alpha release from plasmacytoid dendritic cells.\textsuperscript{40}

In summary, a genetic complement deficiency may contribute to the cause of SLE through the defective clearance of both apoptotic cells and immune complexes. Alternatively, or in addition, complement deficiency may promote a loss of tolerance to autoantigens through effects on both lymphocytes and antigen-presenting cells. None of these possibilities are mutually exclusive. An acquired hypocomplementaemia, due to active lupus, may serve to exacerbate disease by similar mechanisms.

**Take home points**

1. A consideration of the complement system is important to those caring for patients with lupus, and for those seeking to understand the pathogenesis.
2. Low levels of C3 or C4, and anti-C1q antibodies are markers of disease activity in lupus. C1q antibodies are correlated with nephritis, but can occur without renal disease in a significant number of patients.
3. Normal levels of C3, C4 and anti-C1q antibodies strongly suggest clinically inactive disease, although abnormal levels may occur with both inactive and active disease.
4. Deposition of complement components in renal and skin biopsy tissue is characteristic of lupus.
5. Although the complement system has well documented proinflammatory functions, the evidence suggests that these may not be an essential part of the effector mechanisms causing tissue damage in lupus. However, the situation is not straightforward, and a proinflammatory role for complement is suggested by some experimental data.
6. Deficiencies of the early classical pathway are strongly associated with lupus, suggesting a protective role for complement. This may be due to defective clearance of immune complexes and/or apoptotic cells leading to increased autoantigen availability, and/or to effects on mechanisms of immunological tolerance.

**Acknowledgement**

I would like to acknowledge the contribution of Mark Walport, who was a coauthor for the first edition of this chapter.

**References**

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest


*This is the first description of anti-C1q antibodies in patients with SLE.*


*This paper is the first in vivo experimental evidence that anti-C1q antibodies are pathogenic.*


*This is the largest prospective study on the clinical utility of complement assays in lupus.*


*This recent paper suggests a new link between deficiencies of the early classical pathway of complement and the pathogenesis of SLE.*
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Introduction

Renal involvement occurs in the majority of patients with lupus sometime during their lifetime. The many variable aspects of nephritis among patients (e.g. the severity of initial inflammation, response to therapy, relapse rate, recurrence following renal transplant) indicate that multiple immunological and non-immunological parameters influence both the initial clinical presentation and the subsequent course.

In general, breakdown in immunological tolerance leads to the production of auto-reactive cells that either through direct infiltration (e.g. T cells, macrophages) and/or through their secretory products (e.g. autoantibodies, cytokines) initiate inflammation. The degree of inflammation is determined by the extent of this invasion along with both the systemic and local response to the assault. The intensity of inflammation coupled with the renal response to these events influences disease severity, the extent of fibrosis and progression to end-stage renal disease.

Immunosuppressive therapy improves renal outcome, although some patients progress to renal failure despite aggressive treatment. When caring for patients with lupus nephritis, it is essential to realize that non-immunological factors (e.g. systemic hypertension and the propensity to develop fibrosis) influence outcome regardless of the initiating events, and therefore, recognition of the contribution of these parameters is essential for effective therapy. Thus, individuals with apparently similar immunological and pathological profiles may progress to renal failure at different rates, despite similar therapeutic interventions.

Each of the above events may contribute to the progressive renal damage associated with lupus nephritis. Pathophysiologically, progressive renal damage may be divided into immune-mediated and non-immune-mediated pathways. Immune-mediated events may be classified as cell-based or small molecule-based. Immune-independent events may be triggered by hypertension or proteinuria. The local renal cellular response to either of these assaults figures influentially in disease progression, response to therapy, and thus overall clinical outcome. Each of these pathophysiological arms of renal damage in lupus nephritis represents a therapeutic target for the clinician. Using this scheme as a backbone, the following discussion will present the pathophysiology of lupus nephritis by linking recognized and proposed therapies to potential mediators in the pathogenesis of lupus nephritis. Nevertheless, these mechanisms occur concurrently, and determining which is most prevalent at any given time in an individual patient is often problematic, and these issues compound therapy in general and application at specific points in times during the course of disease in individual patients, in particular.
Immune-mediated pathways: cell-based

Cell-based destructive pathways in lupus nephritis begin with autoreactivity. Autoreactive cells in lupus nephritis include T cells, B cells, macrophages and dendritic cells. Autoreactivity is genetically determined but activated through environmental triggers. It manifests with the production of pathological autoantibodies, immune complex formation in tissue (e.g. the kidney), activation of complement, Fc receptor cellular engagement and triggering of the local inflammatory cascade.

Both the systemic and local responses are influenced by genetic factors. In this regard, multiple genes are operative and influence both susceptibility to lupus in general, and nephritis in particular. Major histocompatibility complex (MHC) and Fc receptor genes have been most extensively studied. Some have been linked to autoantibody production and disease, although the associations vary with the population under study. Inherited deficiencies in complement components, including those coded within and outside the MHC region have also been linked to lupus with variable rates of expression of nephritis.

Among those with lupus nephritis, the propensity to develop progressive renal failure is also influenced by genetic factors. For example, progressive renal disease is more common among males and non-Caucasians.

Murine models of spontaneous lupus provide insights. Both the development and severity of nephritis are under the influence of multiple genes. Some strains are more likely to develop autoreactivity than others, and, among those strains, the propensity to develop nephritis is genetically determined. Analogous to human lupus, both MHC and non-MHC loci and genes have been linked, and the severity of inflammation and the propensity to develop fibrosis are under the influence of multiple genes (Table 4.1). In this regard, the powerful experimental approach of breeding synthetic animals (knockout, transgenic, point mutation, etc.) has revealed numerous

### Table 4.1 Selected genes or loci associated with human or murine lupus nephritis

<table>
<thead>
<tr>
<th>Species</th>
<th>Number of mapped or associated genes or loci</th>
<th>Examples</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human gene or polymorphism</td>
<td>24</td>
<td>FcγRIIIA, B, IL-8, PAI-1, MCP1 are all kidney-specific and associated with lupus nephritis</td>
<td>65</td>
</tr>
<tr>
<td>Murine loci</td>
<td>34</td>
<td>Sle1 and Nba2 (nephritis in murine lupus), Agnz1 (acute nephritis), Cgnz1 (chronic nephritis)</td>
<td>66</td>
</tr>
<tr>
<td>Loci important in humans with recognized murine homologues</td>
<td>5</td>
<td>CRPISAP (human) and Sle1/Nba2 (murine)</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FCγRIIA/IIA (human) and Nba2 (murine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PDCCI (human) and Bxx3 (murine)</td>
<td></td>
</tr>
</tbody>
</table>
murine candidate genes for lupus and includes alleles coding proteins that function in antigen or immune complex clearance, lymphoid signalling and apoptosis. Each protein participates in a spectrum of unique and/or integrated signalling pathways, underscoring the complex interactions that underlie the development of clinical disease. Further identification of these genetic factors and their biological interactions should have an impact on therapy by providing information relevant to who will develop nephritis, respond to specific forms of therapy and develop progressive renal failure.

These considerations provide the rationale for therapies targeted at immune and inflammatory cells that either produce soluble mediators, engage cells that mediate this function or directly participate in renal infiltration. Targeting these cells and pathways are discussed in subsequent sections (Table 4.2).

**Inhibitors of cell-based destructive pathways**

**Glucocorticoids.** Glucocorticoids limit tissue infiltration of activated T cells by acutely increasing apoptosis and suppressing proliferation – the latter at least in part by inhibiting interleukin (IL)-2, which is a major T cell growth factor. Limiting T cell activation, in turn, limits B cell and macrophage activation. Glucocorticoids directly decrease monocyte infiltration, reduce the expression of adhesion molecules, and decrease cytokine and chemokine production from sites of inflammation. The latter is relevant to the postulated direct role of macrophages in the pathogenesis of lupus nephritis. In this regard, the interstitial nephritic lesions consist of activated macrophages where they express proinflammatory and fibrogenic cytokines, further exacerbating cellular infiltration and inflammation.

**Cyclophosphamide (CTX), mycophenolate mofetil (MMF) and azathioprine (AZA).** These agents inhibit cell-based inflammatory pathways by directly blocking production of T and B cells (e.g. in the bone marrow). This has the effect of decreasing the number of potential infiltrating autoreactive cells, as well as blunting proliferation of autoantibody producing B cells (i.e. directly and indirectly by suppressing T cell co-stimulation pathways).

CTX is an alkylating agent that inhibits DNA synthesis and mitosis by forming covalent bonds with the oxygen and nitrogen substituents on guanine and adenine residues. MMF is a specific inhibitor of inosine monophosphate dehydrogenase and impairs de novo purine synthesis in both T and B lymphocytes. The drug also interferes with the expression of adhesion molecules, which may further limit cellular infiltration and the inflammatory response.

MMF inhibits induction of inducible nitric oxide synthase, which limits oxidative damage from infiltrating cells. AZA is a purine analogue that is converted to the active drug (6-mercaptopurine (6-MP)) by the liver. The enzyme hypoxanthine-guanine phosphoribosyl transferase converts 6-MP to a nucleotide, which is incorporated into DNA. The abnormal nucleotide is recognized as a mismatch by the cell’s intrinsic repair system, which triggers apoptosis. Taken together, each of these agents blunt cell-mediated destructive pathways by decreasing the number of circulating autoreactive cells with declines in autoreactive events. MMF may also decrease inflammation through additional cell-independent pathways.
Table 4.2 Biological inhibitors of lupus activity

<table>
<thead>
<tr>
<th>Therapeutic inhibitor</th>
<th>Biological targets</th>
<th>Clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucocorticoids</strong></td>
<td>All cell lines</td>
<td>Limits tissue infiltration via increased apoptosis and suppressed proliferation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limit T and B cell activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decrease monocyte infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce the expression of adhesion molecules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decrease cytokine and chemokine production</td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>All cell lines</td>
<td>Decreased bone marrow production of all cell lines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alkylating agent that inhibits DNA synthesis</td>
</tr>
<tr>
<td><strong>Mycophenolate mofetil</strong></td>
<td>T and B cells</td>
<td>Impairs de novo purine synthesis in both T and B lymphocytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interferes with the expression of adhesion molecules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibits nitric oxide, limiting oxidative damage from infiltrating cells</td>
</tr>
<tr>
<td><strong>Azathioprine</strong></td>
<td>T and B cells</td>
<td>Purine analogue recognized as a mismatch triggering apoptosis</td>
</tr>
<tr>
<td><strong>Rituximab</strong></td>
<td>CD20</td>
<td>Chimeric monoclonal antibody against CD20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Results in both complement and FcγR-mediated cell killing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduces circulating B cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical efficacy unclear, optimistic results from several small trials</td>
</tr>
<tr>
<td><strong>Infliximab, etanercept</strong></td>
<td>Tumour necrosis factorα (TNFα)</td>
<td>Blocks TNFα-mediated release of regulatory cytokines liberated by dendritic cells and macrophages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Safety of TNF inhibition in lupus nephritis is an issue</td>
</tr>
<tr>
<td><strong>Sifalimumab</strong></td>
<td>Interferon α (IFNα)</td>
<td>Inhibits IFNα-induced breakdowns in tolerance by neutralizing overexpression of IFN-inducible genes, including BAFF, TNFα, IL-10, IL-1 and GM-CSF</td>
</tr>
<tr>
<td><strong>Tocilizumab</strong></td>
<td>IL-6 receptor</td>
<td>Prevents B cell maturation into plasma cells, interrupting antibody</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In clinical trials, reduces inflammatory markers and autoantibody levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side effects include neutropaenia and infection</td>
</tr>
</tbody>
</table>
Table 4.2 (continued) Biological inhibitors of lupus activity

<table>
<thead>
<tr>
<th>Therapeutic inhibitor</th>
<th>Biological targets</th>
<th>Clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epratuzumab</td>
<td>CD22</td>
<td>Anti-CD22 antibody that modulates mature B cell function without causing depletion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blocks in vitro proliferation of CD27+ and CD27− B cells from SLE patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical trials of patients with lupus flares effective in reducing symptoms and steroid doses</td>
</tr>
<tr>
<td>Belimumab</td>
<td>BLyS</td>
<td>BLyS concentration associated with disease activity and anti-dsDNA titres in lupus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phase III trials belimumab resulted in a significant reduction in lupus symptoms</td>
</tr>
<tr>
<td>Abatacept</td>
<td>CTLA4</td>
<td>Soluble fusion protein engages CD28 ligands and downregulates T cell activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two trials assessing the effect of abatacept in lupus nephritis are currently ongoing</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Reactive oxygen species (ROS)</td>
<td>Precursor of the free radical scavenger glutathione</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreases ROS from T cell necrosis in lupus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Currently under study in the treatment of patients with lupus</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>mTOR</td>
<td>Inhibits effects of mTOR, which in lupus includes increased calcium flux following activation of the TCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Also improves dysfunctional TCR signalling with activation of autoreactivity, and may influence T cell differentiation and function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rapamycin shown to be beneficial in a small pilot study in lupus patients</td>
</tr>
<tr>
<td>Fostamatinib</td>
<td>SyK</td>
<td>Blocks aberrant signalling via the TCR associated with Syk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syk inhibitor shown to be beneficial in patients with rheumatoid arthritis</td>
</tr>
</tbody>
</table>

*Rituximab.* Rituximab is a chimeric (e.g. human–mouse) monoclonal antibody against CD20, a four-transmembrane spanning molecule expressed on B cells at late pre-B cell stage (in the bone marrow) and during differentiation and development in the periphery.\(^ {19}\) CD20 is not present on mature plasma cells. Binding of rituximab to CD20+ cells results in both complement and FcγR-mediated cell killing, and, clinically, is an effective depleter of these cells.\(^ {19}\) A reduction of circulating B cells would be expected to decrease cellular infiltration of the kidney as well as quench the production...
of pathological autoantibodies. B cell depletion prevents the development of murine lupus nephritis, and this effect was not totally dependent on autoantibody production. In human trials, the clinical efficacy of rituximab remains unclear, with optimistic results from several small trials but no apparent effect in a phase II/III double blind, placebo controlled trial.\(^20\) Despite the lack of clear clinical efficacy for B cell depletion, B cells remain vital components in the development of end organ dysfunction in lupus through the production of pathogenic autoantibodies and as antigen-presenting cells for autoreactive T cells.

**Immune-mediated pathways: small molecule-based**

Defective peripheral B cell tolerance is a major feature of lupus-prone mouse strains and activation of autoreactive B cells via T cell-dependent and independent means results in B cell activation and autoantibody production. Autoreactive B cells may also serve as antigen-presenting cells to activate autoreactive T cells. These activated T cells play a direct role in renal inflammation (e.g. interstitial nephritis),\(^21\)–\(^24\) and, if unregulated, this interaction of autoreactive B and T cells will further augment the autoimmune response. In this regard, the presence of B cells within interstitial and peri-vascular infiltrates in the kidney suggests a role as antigen-presenting cells to autoreactive T cells, whereas mice without B cells lacked the infiltrates.\(^25\) This is further supported by the presence of interstitial nephritis and vasculitis in genetically manipulated lupus-prone mice (e.g. they express membrane-bound immunoglobulin (Ig) on B cells, but do not secrete Ig).

The most proximal step in the activation of small molecule-based immune-mediated pathways in lupus nephritis is the development of nephritogenic lupus autoantibodies. Patients with lupus spontaneously produce autoantibodies that react with a variety of cellular and extracellular constituents, including DNA and other nucleic acids, nucleoproteins, cytoplasm components, cell surface antigens and matrix components.\(^26\)–\(^31\) These immunoglobulins participate in the formation of immune deposits,\(^32\) and this is presumed to be the initial event in the inflammatory process.

Nephritogenic antibodies are usually IgG and many (but not all) react with autoantigens, including intracellular and extracellular antigens.\(^33\) Three general theories have emerged on how these antibodies form deposits: 1) deposition of preformed circulating immune complexes, 2) direct binding of autoantibodies to intrinsic glomerular antigens and 3) binding of autoantibodies to autoantigens previously complexed to glomerular antigen.

Correlation of circulating immune complex levels and nephritis (in experimental models of lupus nephritis) led to the conclusion that the deposition of complexes was the proximate cause of disease.\(^34\) However, it has been difficult to demonstrate that deposition of preformed circulating immune complexes initiates nephritis. Nevertheless, immune complexes activate glomerular cells (e.g. mesangial and endothelial cells),\(^35\) and therefore it is likely that this phenomenon contributes to inflammation once it is initiated. Immune complexes may also bind to pre-existing complexes to perpetuate disease, although this mechanism has not been fully explored. Most evidence supports the initiation of immune deposits by *in situ* mechanisms, through the direct binding
of autoantibodies to either intrinsic glomerular antigens or circulating autoantigens with an affinity for glomerular determinates. In the former case antibodies eluted from lupus kidneys have been observed to directly bind to extracellular glomerular constituents or, in the latter, anti-DNA, anti-histone and anti-nucleosome antibodies may bind to nucleosomes or the glomerular basement membrane (GBM) with the exposed DNA acting as a planted antigen for subsequent binding by anti-DNA antibodies. 

The formation of immune deposits is also affected by differences in the pathological potential of lupus autoantibodies. In addition, among the autoantibodies that form deposits, the location of the deposited antibody may vary (e.g. either mesangial, subendothelial, basement membrane or intraluminal deposits) and be associated with differences in clinical presentation. In this regard, direct interaction of individual autoantibodies with either mesangial, endothelial or epithelial cell membranes produced immune deposits at different locations and this was associated with differences in disease expression by light microscopy and clinical proteinuria. Variations in disease expression are also due to differences in both the recruitment of inflammatory mediators, and direct interactions of autoantibodies with cell surface and basement membrane constituents, suggesting that differences in the autoantibody profile among individuals with lupus are likely to contribute to the differences in disease expression.

Taken together, the above evidence suggests that the activation of small molecule-based immune-mediated pathways in lupus nephritis begins with the production of nephritogenic lupus autoantibodies followed by the formation of immune deposits with the subsequent initiation of the inflammatory process. Cellular infiltration and activation are central to these pathological processes, but in the context of the inflammatory response, the modulation of these events is mediated by inflammatory cytokines and small molecules, many of which are therapeutic targets in lupus.

**Inhibitors of cytokines**

Cytokine and/or small molecule activation in lupus result(s) from the inflammatory response and may be the result of one or many stimulatory pathways. The design of antagonists of individual cytokines or small molecules is based on the rationale that interruption of a specific pathological pathway will alleviate downstream inflammatory events and translate into improved clinical outcome. The large number of inhibitors currently available or under study also provides a unique opportunity to consider the pathophysiology of lupus nephritis in the context of new therapeutic approaches to the disease. Cytokine blockers include inhibitors of tumour necrosis factor (TNF), interferon and the IL-6 receptor.

Preventing structural damage from first and subsequent lupus flares is essential for improving long-term outcome. Thus, the redundancy of activated cytokine and chemokine networks in lupus may limit the effectiveness of drug therapy directed at only a single cytokine or molecule, and suggests the need for concurrent inhibition of multiple targets or pathways. On this basis, future therapeutic approaches to lupus nephritis are likely to be tailored to the level of ongoing autoimmunity, extent of clinical symptoms and/or degree of irreversible structural damage.
Infliximab and etanercept. Inhibitors of TNF include infliximab and etanercept. TNF is a proinflammatory and regulatory cytokine liberated by dendritic cells and macrophages. In some animal models TNF aggravates nephritis, and in humans TNF levels are increased. The safety of TNF inhibition in lupus nephritis has been brought into question due to serious side effects (reviewed in). In this regard, TNF inhibition in rheumatoid arthritis was associated with the formation of autoantibodies and/or development of systemic lupus erythematosus (SLE). In murine models, TNF may both inhibit autoimmunity and foster the development of inflammation, suggesting that blocking anti-inflammatory effects must be balanced with the risk of amplified inflammation. Similarly, anti-cytotoxic T lymphocyte antigen (CTLA) 4 antibody treatment for melanoma was associated with the de novo development of lupus nephritis. Taken together, these observations underscore the complex and paradoxical biological effects of some mediators of autoimmunity and indicate potential therapeutic limitations of their inhibitors.

Sifalimumab. Interferon α (IFNα) is liberated by circulating mononuclear cells in some patients with lupus and elevated levels may be associated with disease activity. Excess IFNα may promote lupus disease activity through a breakdown in tolerance via its effects on dendritic cells, T and B cells. Anti-IFNα monoclonal antibody (sifalimumab) was shown in a phase I study to neutralize overexpression of IFN-inducible genes, including a beneficial effect on downstream signalling pathways mediated by BAFF (B cell activating factor belonging to the tumour necrosis factor family), TNFα, IL-10, IL-1 and granulocyte macrophage colony stimulating factor (GM-CSF). BAFF plays an important role in survival and homeostasis of peripheral B cells, especially autoreactive B cells. IL-10 inhibits T cell function and several proinflammatory cytokines, but also promotes B cell-mediated functions enhancing survival, proliferation, and differential and antibody production. IL-1 is a major mediator of inflammation with basic roles in tissue repair and host defence. Increased levels, however, may be associated with pain, fever and anorexia, as well as deleterious effects on endothelial cells (i.e. vasculitis and thrombosis), and the promotion of destructive bone and joint disease. GM-CSF influences the pathogenesis of lupus nephritis by triggering chemokine expression from monocytes. Taken together, IFNα inhibition may significantly influence several important inflammatory pathways mediating the development of lupus nephritis.

INFγ is a major Th1 cytokine that promotes development of nephritis in murine lupus. In this regard, the balance between Th1 and Th2 cytokines may be relevant in the pathogenesis of lupus nephritis, with an increased ratio favouring nephritis. There are no clinical blockers of INFγ currently in use, but novel approaches to blocking the cytokine in animal models continue.

Tocilizumab. IL-6 is a proinflammatory cytokine that induces B cell maturation into plasma cells and augmentation of antibody production. IL-6 plays an important role in the pathogenesis of murine lupus glomerulonephritis, and in humans, IL-6 levels correlate with disease activity and anti-DNA levels. Blockage of IL-6 receptor function with tocilizumab was associated with a reduction in inflammatory markers and autoantibody levels. Disease activity was also improved, but side effects included neutropaenia and high rate of infection.
Inhibition of small molecules

Small molecule inhibitors include antagonists of B cells, inhibitors of T cell co-stimulation and compounds that directly target T cells. B cell depletion with rituximab is discussed above and modulates the pathogenesis of lupus by decreasing cellular proliferation and thus infiltration. This approach also decreases autoantibody production.

Epratuzumab. Epratuzumab is an anti-CD22 monoclonal antibody that modulates mature B cell function without causing depletion. CD22 is found on mature and memory B cells, thus epratuzumab targets these groups, sparing developing and antibody secreting B cells. In vitro treatment of B cells with epratuzumab also blocks proliferation of both CD27+ and CD27– B cells from SLE patients. In two clinical trials of patients with lupus flares, epratuzumab was effective at reducing symptoms and steroid doses, with an acceptable safety profile.

Belimumab. The B lymphocyte stimulator (BLyS) is an important cytokine for the survival of B cells and may be overexpressed in lupus patients. The concentration of BLyS is associated with disease activity and anti-dsDNA titres in lupus, and its activity is blocked by belimumab. Belimumab is also associated with a reduction in CD20+ lymphocytes and short-lived plasma cells, as well as a decrease in anti-dsDNA antibody levels. In phase III trials, belimumab resulted in a significant reduction in lupus symptoms, was well tolerated and had a favourable side effect profile, raising hopes that it may be the next small molecule approved for therapy of lupus.

Abatacept. Inhibition of T cell co-stimulation of B cells represents an additional approach to abrogating the pathological cascades in lupus. T cell co-stimulation of B cells results from helper T cell activation following recognition of antigen on the surface of B cells. With activation, these T cells synthesize effector molecules synergizing in B cell activation. In this regard, CD40 ligand (CD40L) is activated on the surface of helper T cells and can engage the CD40 receptor on B cells. When combined with antigen binding, the CD40L–CD40 interaction promotes B cell activation, proliferation and maturation into plasma cells. Activated B cells express additional co-stimulatory molecules that engage CD28 on the surface of T cells that enhances B cell–T cell interactions, as well as driving additional T cell activation. CD28 ligands also recognize the CTLA4 receptor, which is expressed on the surface of activated T cells. Abatacept is a soluble fusion protein consisting of the extracellular domain of CTLA4 and the constant portion of immunoglobulin. The agent engages CD28 ligands expressed on the surface of T cells, and thus downregulates T cell activation by disrupting CD28 co-stimulatory interactions. A phase II trial in patients with non-renal lupus demonstrated no differences in lupus flares but an increase in serious side effects in abatacept-treated patients. Two trials assessing the effect of abatacept in lupus nephritis are currently ongoing.

N-acetylcysteine. Necrotic death of T cells (as opposed to programmed cell death (apoptosis)) is proinflammatory and a feature of T cells from lupus patients. Mitochondrial dysfunction with ATP depletion and increased reactive oxygen species contributes to T cell necrosis in lupus. In this regard, N-acetylcysteine, a precursor of the free radical scavenger glutathione, improves murine lupus and is currently under study in the treatment of patients with lupus.
Rapamycin. In addition to the production of reactive oxygen species, activation of the mammalian target of rapamycin (mTOR) may be dysfunctional in lupus. mTOR is an important signalling protein in T cells and may regulate calcium flux following activation of the T cell receptor (TCR). In this regard, T cells from SLE patients demonstrated increased intracellular calcium levels after TCR stimulation and these changes were blocked by the mTOR inhibitor, rapamycin. TCR signalling in lupus is dysfunctional and may lead to the inappropriate activation of autoreactivity. In addition, mTOR activity is increased in lupus with regulation of several atypical signalling proteins associated with the TCR. mTOR also influences T cell differentiation and function, and also affects monocytes, dendritic cells and cytokine activities. Rapamycin has been shown to be beneficial in murine lupus, and in a small pilot study in lupus patients. It is currently undergoing continued clinical testing.

Fostamatinib. A downstream mediator of mTOR is spleen tyrosine kinase (Syk), which influences the development of T and B cells. In lupus T cells, Syk participates in aberrant signalling via the TCR, and treatment with the Syk inhibitor R788 (fostamatinib) significantly delayed the development of renal pathology and mortality in a murine model of lupus and was shown to be beneficial in patients with rheumatoid arthritis.

Non-immune-mediated pathways: hypertension and proteinuria

Hypertension and proteinuria are recognized risk factors for disease progression in patients with chronic kidney disease. The structural damage resulting from lupus nephritis reduces nephron mass and should be assumed to place the patient at risk for progressive renal damage. In this regard, a loss of greater than 50% functioning nephron mass results in glomerular hypertension, activation of the renin–angiotensin–aldosterone system, hypertension, proteinuria and hyperlipidaemia. These maladaptations lead to upregulation of proinflammatory cytokines, progressive glomerulosclerosis and interstitial fibrosis, and a further reduction in viable kidney tissue. Clinically, hypertension and proteinuria are the most critical clinical targets for slowing the loss of function.

Hypertension. Control of systemic hypertension slows the rate of loss of kidney function. Angiotensin II blockade with either angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are first-line therapy for blood pressure control in patients with chronic renal disease. Current blood pressure targets are less than 130/80 mmHg. Sodium reduction, loop diuretics, beta blockers and calcium channel blockers may also be required to attain blood pressure goals. Dihydropyridine calcium channel blockers are effective anti-hypertensive agents that should be used with the co-administration of ACE inhibitors or ARBs.

Proteinuria. Proteinuria is an independent risk factor for progressive loss of renal function. Lupus nephritis includes glomerulonephritis, and glomerular scarring following successful treatment of a lupus flare may increase proteinuria. Reduction of albuminuria with ACE inhibitors or ARBs slows the loss of renal function in both diabetic and non-diabetic patients. Target levels of 300–500 mg/day may be associated with slowing of progression. When combined with ACE inhibitor or ARB therapy,
Aldosterone inhibition with spironolactone may further reduce blood pressure and proteinuria; however, hyperkalaemia is a significant potential complication. Finally, dietary protein restriction to approximately 0.8–1.0 mg/kg/day has been shown to reduce the rate of loss of kidney function.

In summary, the pathogenesis of lupus nephritis is the culmination of a series of inflammatory events mediated by cells, cytokines and other small molecules (Table 4.3). Selected steps in this pathway may be amenable to interruption through specific and non-specific forms of drug therapy. However, renal failure of lupus nephritis may begin with autoimmunity and inflammatory damage to the kidney, but in the end may be driven by non-immunological factors such as hypertension and proteinuria, both of which may be favourably modulated with appropriate therapy.

Conclusions
Multiple cells and soluble factors participate in the initiation and perpetuation of lupus nephritis. Variable disease expression, responsiveness to therapy and disease progression commonly observed among patients is typical: this is both genetically determined and under the influence of environmental and exogenous factors. In human lupus, T cell-dependent, autoantibody production leads to antibody deposition, and this is associated with cellular infiltration and activation/proliferation of endogenous renal cells. Disease severity is determined by the nature and intensity of the autoimmune response and the intensity of renal inflammation; the latter are influenced by systemic and local (within the kidney) factors. Renal cells participate in augmenting inflammation and fibrosis. In lupus patients, disease progression is determined by the effectiveness at which therapy modulates both the systemic autoimmune, nephritogenic response and the local renal inflammatory, fibrogenic process.

We anticipate that the therapeutic approach to lupus nephritis will continue to evolve based on the above principles, augmented by the application of strong molecular tools such as transcriptional profiling (i.e. DNA microarrays) and the recognition of biomarkers of disease activity.

Take home points
1. Autoreactive cells through direct infiltration and/or through their secretory products initiate inflammation in lupus nephritis. Immunological and non-immunological factors influence outcome in lupus nephritis, and these pathophysiological arms of renal damage represent therapeutic targets.

2. Cell-based destructive pathways include autoreactive T cells, B cells and macrophages manifesting with the production of pathological autoantibodies, immune complex formation, activation of complement and triggering of the local inflammatory cascade. In murine models, both the development and severity of nephritis are under the influence of multiple genes and both MHC and non-MHC loci and genes have been linked.

3. Glucocorticoids limit tissue infiltration of activated T cells by increasing apoptosis and suppressing proliferation. CTX, MMF and AZA inhibit cell-based inflammatory pathways by directly blocking production of T and B cells (e.g. in the bone marrow).
### Table 4.3 Pathogenic mediators in the development of lupus nephritis

<table>
<thead>
<tr>
<th>Group</th>
<th>Mediator</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibodies</strong></td>
<td>AutoAb/IgG</td>
<td>Type and severity of disease associated with Ig deposition, isotype, location and quantity of immune deposits</td>
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<tr>
<td></td>
<td></td>
<td>Autoantibodies (some but not all) produce nephritis after transfer to normal animals</td>
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<td></td>
<td></td>
<td>Lupus-prone mice without CD40L do not get nephritis</td>
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<tr>
<td><strong>FcR</strong></td>
<td>FcR phenotype associated with lupus and lupus nephritis in some populations but not others</td>
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<tr>
<td></td>
<td>Lupus-prone mice without FcR have reduced nephritis, despite Ig deposition</td>
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<tr>
<td></td>
<td>Treatment of lupus-prone mice with high dose GCSF results in FcRγIII expression and less disease</td>
<td></td>
</tr>
<tr>
<td><strong>Cells</strong></td>
<td>Macrophages</td>
<td>Activated macrophages are present within interstitial lesions, where they express proinflammatory and fibrogenic cytokines</td>
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<tr>
<td></td>
<td>Transfer of macrophages exacerbates disease</td>
<td></td>
</tr>
<tr>
<td><strong>T cells</strong></td>
<td></td>
<td>Prognosis associated with severity of interstitial nephritis, in part due to cellular infiltration</td>
</tr>
<tr>
<td></td>
<td>Interstitial infiltrates in human lupus consist of macrophages and T cells</td>
<td></td>
</tr>
<tr>
<td><strong>B cells</strong></td>
<td></td>
<td>B cells produce pathogenic autoantibodies and serve as antigen presenting cells for autoreactive T cells. Defective peripheral B cell tolerance is a major feature of lupus-prone mouse strains. Autoreactive B cells may also serve as antigen-presenting cells to activate autoreactive T cells. Interstitial nephritis and vasculitis in genetically manipulated lupus-prone mice, they express membrane-bound Ig on B cells but do not secrete immunoglobulin</td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td></td>
<td>Cytokine and chemokine overexpression/suppression in lupus-prone mice alters disease by influencing both systemic autoimmunity and local inflammation</td>
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<tr>
<td></td>
<td>In sclerotic areas, TGF-β receptors are increased in mesangial cells and epithelial cells</td>
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<tr>
<td></td>
<td>IFNγ, MIP-1, MCP 1, CSF-1, TGF-β, PDGF and TNFα implicated in lupus nephritis, whereas Rantes, IL-8 and others have mediated inflammation and fibrosis in other models of nephritis</td>
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<tr>
<td></td>
<td>Perforin is decreased in murine lupus nephritis</td>
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<tr>
<td></td>
<td>MIP-1 and MCP 1 are upregulated in human nephritis via CCR5</td>
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<tr>
<td></td>
<td>Proinflammatory cytokines (e.g. TNF, sVACM, increased in urine of patients with lupus nephritis)</td>
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<td></td>
<td>Procoagulants (e.g. plasminogen) upregulated in lupus nephritis</td>
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</tbody>
</table>
Table 4.3 (continued) Pathogenic mediators in the development of lupus nephritis

<table>
<thead>
<tr>
<th>Group</th>
<th>Mediator</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>In lupus-prone mice, therapy directed at interruption of</td>
<td>Either cyclosporine or thymectomy prevents disease in some</td>
</tr>
<tr>
<td>molecules</td>
<td>cellular interaction involving T cells reduces disease activity</td>
<td>lupus-prone strains</td>
</tr>
<tr>
<td></td>
<td>(e.g. CD40–CD40L, CTLA4Ig, anti-LFA 1, anti-ICAM)</td>
<td>Lupus-prone mice without class II molecules have reduced autoantibodies and nephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment of lupus-prone mice with either anti-LFA 1 or anti-ICAM attenuates nephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Class II, CD40 increased in renal tubular epithelial cells in lupus nephritis</td>
</tr>
</tbody>
</table>

4. Rituximab is a chimeric monoclonal antibody against CD20 and is an effective depleter of B cells.

5. The most proximal step in the activation of small molecule-based immune-mediated pathways is the development of nephritogenic lupus autoantibodies that participate in the formation of immune deposits. The use of antagonists of individual cytokines or small molecules is based on the rationale that interruption of a specific pathological pathway will alleviate downstream inflammatory events and translate into improved clinical outcome.

6. Inhibitors of cytokines and small molecules of interest in the therapy of lupus nephritis include infliximab and etanercept (TNF), sifalimumab (anti-IFNα tocilizumab (IL-6 receptor), epratuzumab (anti-CD22), belimumab (BLyS), abatacept (inhibits T cell co-stimulation of B cells), N-acetylcysteine (free radical scavenger), rapamycin (engages mTOR) and fostamatinib (Syk inhibitor).

7. Non-immunological disease progression in lupus manifests clinically as hypertension and proteinuria, both of which are treated using ACE inhibitors or ARBs.

References

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest


*An excellent review of MMF and belimumab in the therapy of lupus nephritis.


**A comprehensive review of B cell biology and associated targets.


*An excellent review of the status of rituximab in the treatment of lupus nephritis.

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** A comprehensive review of the current state of biologic therapy of lupus nephritis.
* A comprehensive review of the role of mTOR and rapamycin therapy in lupus.


   *An excellent summary of the complexities and our understanding of the genetics of human lupus nephritis.*


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Introduction

Systemic lupus erythematosus (SLE) is an inflammatory disease characterized by a significant disease-related morbidity and mortality, and also adverse side effects associated with drug therapy. Clinically apparent nephritis develops in about 40–75% of patients with lupus and the kidney is the organ most commonly affected. The overall survival of patients with SLE and a proliferative glomerulonephritis (World Health Organization (WHO) classes III and IV) has improved considerably over the last few decades. The improved survival is due to a combination of factors: including the wider use of corticosteroids and immunosuppressants and the availability of more effective anti-hypertensive drugs, antibiotics, renal dialysis and transplantation. Nevertheless, after 10 years of treatment 5–10% of patients have died and a further 5–15% developed end-stage renal failure. Early deaths from extra-renal lupus and infection are now uncommon but, instead, renal failure and cardiovascular disease have emerged as important determinants of morbidity and mortality. Adverse prognostic factors for renal function and death include renal impairment and hypertension at the time of diagnosis, chronic damage on a renal biopsy, African American ethnicity, failure to induce remission and renal flares.

Lupus nephritis

Diagnosis of lupus nephritis is confirmed by renal biopsy in patients with a nephritic urine sediment (proteinuria, haematuria and red cell casts) or with proteinuria in excess of 0.5 g/day. Three major patterns of lupus nephritis have been defined, based on renal histology: focal proliferative, diffuse proliferative and membranous glomerulonephritis. This classification has subsequently been expanded by a WHO committee and was revised in 2003 by the International Society of Nephrology and the Renal Pathology Society. (See Chapter 2) Most treatment studies used the WHO classification and hence these will be highlighted. Patients with minimal changes or mesangial glomerulonephritis (WHO class I and II lesions) usually have an inherently low rate of progressive renal failure. Patients with membranous nephropathy (WHO class V) have an intermediate prognosis for renal function. By contrast, patients with focal or diffuse proliferative glomerulonephritis (WHO class III and IV) have a high risk of progressive renal failure.
General approach to the therapy of lupus treatment

The majority of patients with SLE are successfully managed with non-steroidal anti-inflammatory agents, hydroxychloroquine and low-dose corticosteroids. Drug regimens are increased in response to flares and gradually tapered during periods of remission. High-dose corticosteroids and immunosuppressive drugs are reserved for patients with life-threatening manifestations including severe lupus nephritis, central nervous system, cardiopulmonary disease or haematological abnormalities such as thrombocytopenia.

As with other proteinuric renal diseases, we recommend angiotensin converting enzyme inhibitors or angiotensin II receptor blockers in patients with lupus nephritis. Angiotensin converting enzyme inhibitor use delayed the development of renal involvement and was associated with a decreased risk of disease activity in SLE. Blood pressure control should aim for a target blood pressure of less than 130/80 mmHg. Hyperlipidaemia should be treated with statins in view of the increased risk of vascular disease in patients with lupus. Finally, we use bone protection in the form of calcium and vitamin D supplements in patients on long-term steroids. Biphosphonates are contraindicated in women of childbearing age.

Treatment of lupus nephritis

There are several considerations in the approach to the treatment of patients with lupus nephritis. The first is based on the histological severity of the renal lesion. The second is based on the severity of the clinical presentation. The third consideration is the choice of therapy for inducing remission of acute disease and for maintaining remission and treating relapses. Several randomized controlled studies have examined the benefits of the addition of immunosuppressants to steroids as compared with steroids alone in the management of the more severe types of lupus nephritis namely membranous and proliferative glomerulonephritis (International Society of Nephrology and the Renal Pathology Society (ISN/RPS) classes III, IV and V). Recent studies have compared the efficacy and toxicity of cyclophosphamide and mycophenolate mofetil (MMF) in the management of lupus nephritis.

Prednisolone

The mainstay of treatment of lupus nephritis is prednisolone. This is given at an initial dose of (0.5–1 mg/kg/day) for 6–8 weeks with gradual tapering to minimize toxicity.

Mesangial proliferative glomerulonephritis (WHO class II/ISN/RPS class II)

Most such patients present with proteinuria and microscopic haematuria, often with little in the way of renal impairment. There are no controlled trials to guide treatment. We treat such patients with corticosteroids (0.1–0.5 mg/kg prednisolone/day tapering over months) in the hope that this will prevent progression to a more severe glomerulonephritis although that is not certain.
Membranous nephropathy (WHO class V/ISN/RPS class V)
The clinical presentation is with proteinuria and in about 50% of cases a nephrotic syndrome. Discussion of the treatment of lupus membranous nephropathy is complicated by the differences between the old WHO classification and the new ISN/RPS classification. In the WHO classification, the frequency of membranous nephropathy was approximately 12% when the definition of the renal histology was confined to pure membranous nephropathy or with mild mesangial hypercellularity, expansion and scattered deposits (WHO classes Va and Vb). The frequency increased to approximately 26% when there was in addition a focal segmental proliferative (WHO class Vc) or diffuse proliferative glomerulonephritis (WHO class Vd).

In older studies, patients with WHO classes Va and Vb were treated with prednisolone and a smaller proportion also received methylprednisolone pulses and oral cyclophosphamide or azathioprine. By contrast, most patients with WHO classes Vc and Vd were treated with cyclophosphamide or azathioprine in addition to prednisolone. With these approaches to treatment, the 10-year survival free of death and renal failure in WHO classes Va and Vb was 72–92%, in WHO class Vc was 40% and Vd was 75%. The current ISN/RPS classification identifies these patients as having a membranous glomerulonephritis plus proliferative glomerulonephritis. In addition to the risk of renal failure, patients with membranous nephropathy are also at risk of developing the complications of a nephrotic syndrome.

In one controlled trial patients with lupus membranous nephropathy were randomized to treatment with prednisolone alone, prednisolone plus cyclosporine or prednisolone plus intravenous cyclophosphamide. All patients received alternative day prednisolone 40 mg/m² body surface area for 8 weeks followed by tapering at 5 mg/week to 10 mg/m² for the remainder of the year. The cyclophosphamide group received intravenous cyclophosphamide 0.5–1.0 g/m² every other month for 12 months. Cyclosporine was given at a dose of 200 mg/m² BSA (approximately 5 mg/kg) and the dose adjusted for rises in serum creatinine. The cumulative probability of remission was 27% with prednisolone, 60% with intravenous cyclophosphamide and 83% with cyclosporine. However, relapses of the nephrotic syndrome occurred significantly more frequently with cyclosporine than with intravenous cyclophosphamide. A recent pooled analysis of patients with lupus membranous nephropathy from two randomized controlled studies showed that prednisolone and mycophenolate mofetil were as effective as prednisolone and intravenous cyclophosphamide in terms of remission induction and stabilization of renal function and survival.

It seems reasonable to treat patients with membranous nephropathy with prednisolone, and if the nephrotic syndrome does not go into remission to add in either mycophenolate mofetil or intravenous cyclophosphamide.

Treatment of ISN/RPS classes IV and V nephritis
In a randomized controlled trial, Bao et al. compared treatment with prednisolone and pulse cyclophosphamide with mycophenolate, tacrolimus and steroids. Complete remission was found at 9 months in 65% of patients treated with the latter regime, compared with 15% of patients treated with steroids and cyclophosphamide.
Mycophenolate mofetil, tacrolimus and steroids appear to be more effective in inducing remission in ISN/RPS class IV and V nephritis than pulse cyclophosphamide and steroids.

**Focal and diffuse lupus proliferative glomerulonephritis (WHO classes III and IV or ISN/RPS classes III and IV)**

The prognosis of patients with focal and diffuse proliferative glomerulonephritis is much poorer than those of patients with mesangial proliferative glomerulonephritis and membranous nephropathy; patients with these renal lesions have been the focus of most of the clinical trials of treatment.

**High-dose intravenous cyclophosphamide for induction—National Institute of Health (NIH) regimen**

The careful randomised controlled studies from the NIH made intermittent intravenous cyclophosphamide and oral prednisolone the accepted method for the management of severe lupus nephritis (WHO classes III and IV).\(^{11**,12**}\) This regime is preferable to continuous oral cyclophosphamide as it typically leads to a lower cumulative dose of cyclophosphamide. From the NIH data, monthly pulse cyclophosphamide (0.5–1.0 g/m\(^2\)) adjusted for the glomerular filtration rate and leucocyte count at 10–14 days is given monthly for the first 6 months, then quarterly for 18–24 months. The longer course of cyclophosphamide was associated with fewer relapses than a shorter 6-month course but is associated with greater gonadal toxicity.\(^{12}\)

A recent meta-analysis of randomised controlled studies\(^{13*}\) has shown that when compared with prednisolone on its own, cyclophosphamide and prednisolone reduced the risk of doubling of the serum creatinine (RR 0.59; 95% CI 0.40–0.88), but not the risk of developing end-stage renal failure (RR 0.98; 95% CI 0.53–1.82) or of death (RR 2.18; 95% CI 1.10–4.34). Cyclophosphamide increased the risk of sustained amenorrhoea (RR 2.18; 95% CI 1.10–4.34). Conversely, azathioprine reduced the risk of death (RR 0.60; 95% CI 0.36–0.99) but had no effect on renal outcomes.

**Low-dose intravenous cyclophosphamide for induction—Euro-Lupus regimen**

The Euro-Lupus study was a randomised controlled trial comparing a low-dose intravenous cyclophosphamide (\(6 \times 500\) mg every 2 weeks) with a modified NIH regimen comprising six monthly infusions and two quarterly infusions of high-dose cyclophosphamide.\(^{14**,15}\) Azathioprine was given to patients after induction from week 12 or 44 in the low-dose and high-dose arms respectively. Death, sustained doubling of serum creatinine and end-stage renal disease rates did not differ between the treatment groups after 10 years of follow-up.\(^{15}\) An early renal response at 6 months predicted a good long-term outcome independent of the initial treatment.

The patients studied were predominantly Caucasians, with mostly normal renal function. This is in contrast to the NIH trials, which enrolled predominantly African American patients who generally have a poorer prognosis. The Euro-Lupus regimen is now accepted as a reasonable alternative to the NIH high-dose cyclophosphamide regimen for the treatment of proliferative lupus nephritis in Europeans.
Mycophenolate Mofetil (MMF) for induction

Mycophenolate mofetil (MMF) inhibits the proliferation of activated B and T cells, antibody formation and the generation of cytotoxic T cells by inhibiting inosine-5’-monophosphate dehydrogenase, involved in the de novo purine synthesis pathway. Mycophenolate mofetil is a powerful immunosuppressant that is licensed for renal transplantation. Pilot studies suggested that it might be effective together with steroids in induction treatment of lupus nephritis and this has now been tested in randomised controlled trials. Chan et al. compared mycophenolate mofetil and prednisolone with prednisolone and oral cyclophosphamide followed by azathioprine in 64 patients with lupus nephritis. In this study the dose and duration of treatment with mycophenolate mofetil was increased in patients who were recruited later. Mean follow-up was 57.8±18.7 months. There was no significant difference in the rates of doubling of serum creatinine, end-stage renal failure and relapses. The risk of amenorrhoea was, however, significantly lower with mycophenolate mofetil than with cyclophosphamide/azathioprine. Ginzler et al. randomised 140 patients with lupus nephritis to treatment with mycophenolate mofetil 3 g/day and prednisolone, or to cyclophosphamide 0.5–1.0 g/m² and prednisolone in a 24-week study. Complete remission (defined as a return to within 10% of normal values of serum creatinine, proteinuria and urinary sediment) was achieved in 16 of 71 patients treated with mycophenolate mofetil (22.5%) and in four of 69 patients treated with cyclophosphamide (5.8%) (p=0.005). On follow-up, there was no difference in the rates of renal relapse, end-stage renal failure or of deaths. Both of these studies excluded patients with severe renal failure.

The Aspreva Lupus Management Study (ALMS) randomized 370 patients with either class III, IV or V nephritis to treatment with mycophenolate mofetil 3 g/day or intravenous cyclophosphamide 0.5–1 g/month for 6 months. All patients also received prednisolone. The trial was powered for superiority of mycophenolate mofetil over intravenous cyclophosphamide. The results showed no difference in renal response between groups (56.2% with mycophenolate mofetil and 53% with cyclophosphamide), serious adverse events (28% mycophenolate mofetil and 23% cyclophosphamide) or infections (69% mycophenolate mofetil and 62% cyclophosphamide). Although superiority of mycophenolate mofetil was not shown, a post hoc subset analysis revealed a difference in response in different ethnic groups. Mycophenolate mofetil was significantly superior to intravenous cyclophosphamide in patients classified as other ethnicity and black patients, with a 60.4% response rate in the mycophenolate mofetil group compared with 38.5% in the intravenous cyclophosphamide group (p=0.033), and also in Hispanic patients (60.9% compared with 38.8% (p=0.011). Mycophenolate mofetil and intravenous cyclophosphamide response rates were similar for Asian and white patients. These findings of superior outcomes with mycophenolate mofetil in black patients need confirmation.

Azathioprine and prednisolone for remission induction in lupus nephritis

Azathioprine is a safe drug and many have argued that it is safer than and probably as effective as cyclophosphamide in the management of lupus nephritis. The study by Grootscholten et al. reported a randomised controlled trial comparing
methylprednisolone, prednisolone and azathioprine with prednisolone and intravenous cyclophosphamide in patients with mostly proliferative lupus nephritis. After a mean follow-up of 5.7 years, azathioprine was found to be less effective, although not significantly so, than cyclophosphamide in reducing the risk of non-sustained doubling of serum creatinine, and was significantly less effective in reducing relapses. An important observation from this study is that cyclophosphamide treatment is more effective in maintaining remission than azathioprine. That is an issue that needs to be addressed when considering the studies of mycophenolate mofetil.

**Remission maintenance treatment**

The most effective treatment for remission maintenance is unclear. In the Euro-Lupus Nephritis Trial, relapses occurred despite ongoing treatment with prednisolone and azathioprine. The study by Contreras et al. in 2004, examined the role of mycophenolate mofetil 0.5–3.0 g/day, azathioprine 1–3 mg/kg/day and 3 monthly intravenous cyclophosphamide (0.5–1.0 g/m²) as maintenance therapy in lupus nephritis patients (mainly WHO classes III and IV). All received induction treatment with 6 months of monthly intravenous cyclophosphamide. The cumulative probability of remaining relapse-free was higher in the mycophenolate mofetil (78%; p=0.02) and azathioprine (58%; p=0.12) groups compared with the cyclophosphamide group (43%) after a median treatment duration of 29, 30 and 25 months. Although there were no significant differences in progression to renal failure, the event-free survival rate for the composite end-points of death and chronic renal failure was higher in the mycophenolate mofetil and azathioprine groups than in the cyclophosphamide group (p=0.05 and p=0.009 respectively). Hospitalization, amenorrhoea and infections were lower in the mycophenolate mofetil or azathioprine groups, compared with cyclophosphamide. The major criticism of this study is that the number of patients studied was relatively small. The MAINTAIN study has just been published which compared azathioprine 2 mg/kg/day or mycophenolate mofetil 2 g/day as maintenance therapy in 105 patients with proliferative lupus nephritis. All received three intravenous pulses methylprednisolone, followed by oral glucocorticoids and six fortnightly cyclophosphamide as induction therapy first. Renal flares were observed in 25% of azathioprine-treated and 19% of mycophenolate mofetil-treated patients, but the difference did not reach statistical significance. Time to renal flare, to severe systemic flare, to benign flare and to renal remission did not statistically differ between the groups. Over a 3-year period, 24 hour proteinuria, serum creatinine, serum albumin, serum C3, haemoglobin and global disease activity scores improved similarly in both groups. Direct comparison of azathioprine and mycophenolate mofetil in remission maintenance is also being evaluated in the maintenance phase of the ALMS trial. In the maintenance phase of the ALMS trial, 226 patients who responded to treatment for six months with either intravenous cyclophosphamide or mycophenolate mofetil were randomised to treatment with mycophenolate mofetil (2 g/day) or azathioprine (2 mg/day). Mycophenolate mofetil was significantly more effective than azathioprine in reducing the risk of treatment failure (hazard ratio, 0.44; 95% confidence interval, 0.25 to 0.77; P=0.003) and time to renal failure and to rescue therapy. This important study shows superiority of mycophenolate mofetil over azathioprine in remission maintenance. Thus, mycophenolate mofetil may have a role as remission maintenance therapy in lupus nephritis but larger randomised controlled studies are needed to confirm this.
Summary of evidence for mycophenolate mofetil use

One can conclude from these studies that mycophenolate mofetil is as effective as cyclophosphamide in patients with mild to moderate lupus nephritis, as current trials have excluded patients with severe lupus nephritis. The ALMS study showed that the incidence of adverse effects appears comparable between mycophenolate mofetil and intravenous cyclophosphamide. Limited data from the ALMS study suggest that mycophenolate mofetil may be superior to cyclophosphamide in black patients but this needs confirmation. Preliminary data suggests that mycophenolate mofetil may be more effective than intravenous cyclophosphamide in remission maintenance.

Treatment recommendations for focal and diffuse lupus proliferative glomerulonephritis (WHO classes III and IV)

Choice of immunosuppressive drug will be influenced by patients’ characteristics, and personal choices. Thus, it may be preferable to favour mycophenolate for remission induction in non-Caucasian/non-Asian patients based on the relative resistance of black patients to intravenous cyclophosphamide shown in two studies. It seems reasonable to use mycophenolate mofetil first in young women, so fertility is not compromised, or alternatively to use the Euro-Lupus regime of short-term low-dose intravenous cyclophosphamide. Whatever treatment is used, assessment of response at 6 months should guide further therapy. Azathioprine seems a reasonable choice for remission maintenance treatment and mycophenolate mofetil can be used in patients unable to tolerate azathioprine.

A summary of the treatment strategies for lupus nephritis is shown in Table 5.1.

Table 5.1 Treatment of lupus nephritis

<table>
<thead>
<tr>
<th>Renal histology</th>
<th>Remission induction</th>
<th>Remission maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial proliferative lupus nephritis (ISN/RPS class II)</td>
<td>Prednisolone*</td>
<td>Not known</td>
</tr>
<tr>
<td>Focal and diffuse lupus nephritis (ISN/RPS class III or IV)</td>
<td>i) Prednisolone plus</td>
<td>Prednisolone plus azathioprine or MMF22</td>
</tr>
<tr>
<td></td>
<td>ii) NIH: monthly intravenous cyclophosphamide for 6 months and every 3 months for 18 months11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>iii) Euro-Lupus intravenous cyclophosphamide 500 mg six doses (every 2 weeks)14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>iv) MMF 3 g/day for 6 months19</td>
<td></td>
</tr>
<tr>
<td>Membranous nephropathy (ISN/RPS class V)</td>
<td>Prednisolone, and if no remission plus MMF8 or intravenous cyclophosphamide 3 monthly for 1 year8</td>
<td>Not known</td>
</tr>
<tr>
<td>ISN RPS V +IV</td>
<td>Prednisolone plus tacrolimus and MMF10</td>
<td>Not known</td>
</tr>
</tbody>
</table>

*Not evidence-based.
**Drug toxicities**

**Cyclophosphamide**
A major side effect is an increased risk of infections (10–18% per year) in particular from herpes. Intravenous cyclophosphamide often leads to nausea and vomiting, but this can be controlled by serotonin antagonists. Damage to the bladder mucosa may cause haemorrhagic cystitis, and subsequent transitional and squamous cell carcinoma. Persistent haematuria, and the absence of lupus activity, should raise suspicion of bladder complications. The use of intravenous cyclophosphamide with vigorous hydration and concomitant administration of mesna has essentially eliminated bladder complications. Prolonged cyclophosphamide is associated with an increased risk of malignancy. Cyclophosphamide is a potent teratogen and must not be used in pregnancy. Cyclophosphamide also causes dose- and age-related gonadal toxicity with oligospermia in men and premature ovarian failure in women. As lupus nephritis chiefly afflicts women of reproductive age, one must balance this risk of premature ovarian failure, which is usually permanent, with the benefits of treatment.

**Mycophenolate mofetil**
Gastrointestinal intolerance, particularly nausea and mild to moderate diarrhoea, occurs in up to 10–40% of patients. There is an increased risk of infections, which can be associated with leucopaenia and lymphopaenia. Mycophenolate mofetil is teratogenic in animal studies and is therefore contraindicated during pregnancy. From case reports, mycophenolate mofetil use during pregnancy appears to be associated with an increased risk of malformations and first-trimester pregnancy loss. The most frequent malformations include cleft palate and lip, microtia, atresia of external auditory canal, micrognathia and hypertelorism. Therefore, mycophenolate mofetil should be discontinued for at least 6 weeks prior to embarking on a pregnancy and be replaced by azathioprine.

**Azathioprine**
Gastrointestinal intolerance and bone marrow toxicity may limit therapy. It can also produce elevation of hepatic enzymes. Other toxicities include an increased risk of infection and the development of malignancies (particularly haemopoietic or lymphoreticular) with prolonged usage. Individuals with thiopurine S-methyltransferase deficiency are more susceptible to marrow toxicity with azathioprine.

**Other therapeutic options**

**Plasma exchange**
Meta-analysis of randomized controlled studies in which plasma exchange was used in addition to azathioprine or cyclophosphamide and prednisolone in patients with lupus nephritis, showed no benefits in terms of mortality (RR 0.71, 95% CI 0.50–1.02), end-stage renal failure (RR 1.24, 95% CI 0.60–2.57) or doubling of serum creatinine (RR 0.17, 95% CI 0.02–1.26). In summary, plasma exchange has no role in the treatment of lupus nephritis.
Intravenous immunoglobulins

Uncontrolled studies have shown a temporary benefit in SLE patients from the infusion of high doses of intravenous immunoglobulin. Currently, there are limited data on the use of intravenous immunoglobulin in the treatment of lupus nephritis and as such this treatment cannot be recommended.

Cyclosporine

Several studies have examined the effectiveness of cyclosporine in the treatment of proliferative lupus nephritis. None of these studies were controlled and it is difficult to discern whether cyclosporine was of any benefit in lupus nephritis. Moroni et al. compared the efficacy of cyclosporine and azathioprine as maintenance agents in 75 patients who had received induction therapy with prednisolone and oral cyclophosphamide for diffuse proliferative glomerulonephritis. At the end of the 4-year follow-up, the reduction in proteinuria and the number of lupus flares was similar in both groups. The nephrotoxicity of cyclosporine is a major problem and, pending randomized controlled studies comparing this drug with other immunosuppressive agents, we cannot recommend its use in proliferative lupus nephritis.

The role of biologicals in the treatment of lupus nephritis

This is described in Chapter 6.

Immune ablation and stem cell transplantation

The reason for haematopoietic stem cell transplantation in association with high-dose immunosuppression in autoimmune disease is to try to reset the immune system and achieve self-tolerance by eliminating autoreactive clones. Procedure-related mortality varies between 5% and 13% among studies, and therefore patient selection is very important. The exact role of autologous stem cell transplant using high-dose cyclophosphamide for SLE has not yet been determined and cannot be recommended.

Immune ablation with high-dose cyclophosphamide

One study examined the effect of high-dose cyclophosphamide without stem cell transplantation. Fourteen patients with moderate-to-severe SLE that had been refractory to corticosteroids and one or more additional immunosuppressive drugs, were treated with 50 mg/kg of cyclophosphamide for 4 consecutive days followed by granulocyte colony-stimulating factor until the neutrophil count was 1×10^9/l for two consecutive days. Patients were followed up monthly for disease activity using the physician’s global assessment, SLE Disease Activity Index and assessment of functioning of involved organs. There were no deaths or fungal infections. Significant improvements in physician’s global assessment, SLE Disease Activity Index, and prednisone dosage were observed. Nine of the 14 patients had renal disease (WHO IV and V); four had complete response, six had a partial response and two patients were unchanged. High-dose cyclophosphamide without stem cell transplantation seems to be a potential alternative in patients with refractory SLE, but long-term follow-up is awaited.
Prognostic factors in lupus nephritis

Patients with proliferative glomerulonephritis (WHO III and IV) tend to have a worse outcome for renal function when compared with patients with milder lesions. The combination of severe active and chronic histological changes on a renal biopsy is also reported to adversely affect outcome.\textsuperscript{2,30}\textsuperscript{*,*} Patients without chronic histological changes, even in the face of active lupus nephritis, had a lower risk of developing renal failure; 90\% or more remaining free of renal failure after 10 years.\textsuperscript{30} A number of clinical variables are associated with a greater probability of renal progression in lupus nephritis. These include: black race, low haematocrit, raised serum creatinine level, presence of hypertension, high urinary protein excretion, low C3 complement and poor socioeconomic status. Failures to respond to prednisolone and cyclophosphamide are also predictors of subsequent development of renal failure, as are nephritic flares.

Dialysis and transplantation

Between 17\% and 30\% of patients with lupus nephritis develop end-stage renal failure by 10 years. Both haemodialysis and continuous ambulatory peritoneal dialysis are well tolerated, and there is a tendency for lupus disease activity to diminish after the start of dialysis. If there is no overt disease activity, then we discontinue immunosuppressants in patients on dialysis and continue with a small dose of prednisolone. Overall survival on dialysis is good, with a 75\% survival at 10 years. Graft survival and function in patients with lupus after transplantation are comparable with those obtained in patients with other diseases and recurrence of lupus nephritis is uncommon after transplantation.

Take home points

1. A summary of the recommendations of the management of SLE is shown in Table 5.1.
2. Complications of drug treatment account for much of the morbidity that develops in SLE, in particular complications of high-dose or chronic corticosteroids (infection, osteonecrosis, osteoporosis, coronary artery disease) and cyclophosphamide (infection, sterility, bladder toxicity and malignancy).
3. It is encouraging that mycophenolate mofetil has a less toxic side effect profile than cyclo-phosphamide.
4. The risk of infections is substantial in patients taking corticosteroids and immunosuppressants.
5. Regular clinical review of the patient’s condition, together with laboratory tests and urinalysis to detect marrow depression, disease activity or progressive disease is mandatory in the management of these patients.

References

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest
REFERENCES

   **Excellent review of lupus nephritis.**

   *Role of scarring in the prognosis of lupus nephritis.*


   **The ISN/RPS classification of lupus nephritis.**


   *First randomized controlled trial of lupus nephritis.*


   **One of a series of studies from the NIH establishing the efficacy of cyclophosphamide in the treatment of lupus nephritis.**

   **Study showing that a longer course of cyclophosphamide is better than a shorter course.**

   *Meta-analysis of treatment of lupus nephritis.*

   **Randomized controlled trial showing that a short course of intravenous low dose cyclophosphamide is as effective as an abbreviated NIH cyclophosphamide regime.**


**First randomized controlled trial to show the efficacy of mycophenolate mofetil in lupus nephritis.**


**Large randomized controlled study comparing mycophenolate mofetil and cyclophosphamide.**


*Comparison of azathioprine versus cyclophosphamide in the treatment of lupus nephritis.*


**Randomized controlled trials of the treatment of the remission phase of lupus nephritis.**


**Prognostic features of renal histology in lupus nephritis.**
Chapter 6

The role of biologics in the treatment of lupus nephritis

Amara N. Ezeonyeji and David A. Isenberg

Introduction

Lupus nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE).\(^1\) Nephritis usually occurs within 5 years of diagnosis and affects up to two-thirds of SLE patients during their disease course.\(^2\)

The prognosis and survival of patients with LN has improved significantly over the last 50 years mainly due to the introduction of corticosteroids (CS), immunosuppressives (ISP) and the increased availability of haemodialysis and transplantation.\(^3\)

Induction therapy with cyclophosphamide (CTX) and CS and maintenance of remission with immunosuppressive drugs was considered the gold standard of therapy in LN, suppressing glomerular inflammation, reducing proteinuria and normalizing renal function.\(^4\)

Induction therapies with CTX and CS have been shown to have improved renal outcomes compared with CS alone. Treatment with CTX is, however, associated with many adverse effects including gonadal toxicity, severe infection and osteoporosis.\(^5\)

Up to 22% of patients with proliferative LN are refractory to therapy with CTX or have recurrent relapses despite repeated treatment.\(^5\) Until recently, for this cohort of patients, the prognosis was bleak with 30% to 50% of patients developing either doubling of creatinine (Cr) or end stage renal failure (ESRF) within 5 years.\(^6,7\) Alternative options such as intravenous immunoglobulin (IVIg), plasmapheresis and high-dose CTX with autologous stem cell transplant, have problems of cost, side effects and/or practicality of treatment. Mycophenolate mofetil (MMF) an inhibitor of T and B cell function has been shown to be as efficacious as CTX in inducing remission. The Aspreva Lupus Management Study (ALMS) assessed the efficacy of MMF as induction treatment in 370 patients with active class III/IV LN, randomized to receive MMF or to intravenous CTX with a tapering dose of oral prednisolone. Overall, 56% of the MMF-treated group responded, compared with 53% of the patients treated with CTX (p=0.575).\(^8\)

Excitingly, treatment aimed at targeting the immunological basis of the disease pathogenesis specifically B and T cell activity, co-stimulatory molecules and antibody production have become increasingly important therapeutic strategies.
Anti-CD20: rituximab

Pathophysiology

The central role for B cells in the pathogenesis of SLE has meant that B cell depletion therapy has become widely used in treatment of LN. Rituximab (RTX) is a chimeric human/mouse monoclonal antibody directed against the B cell surface marker CD20 found on pre-B cells maturing to memory B cells (but not on stem cells, pro B cells or plasma cells). RTX was initially approved for the treatment of non-Hodgkin’s lymphomas and subsequently for rheumatoid arthritis (RA). RTX has subsequently been widely used off label to treat many autoimmune conditions of likely or proven B cell origin.\textsuperscript{9–11} RTX treatment leads to profound depletion of B cell subsets.\textsuperscript{12} *In vitro* B cell depletion occurs through antibody-dependent cell-mediated and complement-dependent cytotoxic mechanisms or apoptosis.\textsuperscript{13,14}

Clinical response

Data on the efficacy of RTX either alone or in combination with CTX in SLE have been reported in small, prospective, open labelled studies reviewed elsewhere.\textsuperscript{3} Studies have shown improvement in a wide spectrum of disease manifestations including arthritis, alopecia, skin disease and renal disease. Evaluation of response has been assessed using global disease activity scores such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI),\textsuperscript{15} or the more detailed British Isles Lupus Assessment Group (BILAG) assessment\textsuperscript{16} with additional assessment of LN by time to achievement of complete (CR, defined as normal serum creatinine, inactive urinary sediment and urinary proteinuria <500 mg/24 hour) or partial remission (PR, defined as >50% improvement in renal parameters that were abnormal at baseline).\textsuperscript{17–19} In all studies, RTX has been shown to be generally safe and well tolerated (Table 6.1).\textsuperscript{20,21}

Clinical trials

Impressive clinical responses with RTX have been reported in open labelled studies. The LUNAR study; a phase III randomized double blinded placebo controlled trials of SLE patients with class II and IV LN treated with MMF and CS who were randomized to receive RTX or placebo failed to meet its primary end-point (the proportion of patients who achieved CR or PR after 52 weeks of treatment).\textsuperscript{**22} A similar failure was seen in the EXPLORER trial for non-renal SLE.\textsuperscript{**23} Failure of these studies may well have been a result of study design. In both, the recruited patients were given relatively high-dose steroids in addition to concomitant ISP such as MMF, which may have obscured the ability of RTX-treated patients to be distinguished from the placebo group.

Although the widespread acceptance of RTX in the treatment of SLE has been compromised by failure of the LUNAR and EXPLORER trials, the fact that rheumatologists around the world have repeatedly noted clinical benefit and the recent success of RTX in the ‘RTX versus CTX as induction therapy in refractory ANCA-associated renal vasculitis’ (RITUXVAS) trial, where the RTX group and the CTX group achieved similar high rates of sustained remission, strongly supports the view that RTX will prove in the long term a useful method of treating active SLE.\textsuperscript{**24}
Table 6.1 A comparison of the treatment protocols and outcomes of five representative studies of B cell depletion

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Diagnosis</th>
<th>Protocol for BCD</th>
<th>Mean disease activity score before/after BCD</th>
<th>BCD/serology changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Looney et al.</td>
<td>18</td>
<td>SLE (seven with LN class III/IV)</td>
<td>RTX 100 mg/m² ×1; or 375 mg/m² ×1; or 375 mg/m² ×4 (weekly); Plus CS Plus baseline ISP</td>
<td>SLAM (8.8±2.3/6.9±4.5 (all patients at 2 months)</td>
<td>BCD: 11/17 Anti-DNA ↔ C3/C4 ↔ Serum creatinine levels within 20% baseline in all subjects</td>
</tr>
<tr>
<td>Sfikakis et al.</td>
<td>10</td>
<td>SLE and class III/IV LN</td>
<td>RTX 375 mg/m² ×4; plus CS 0.5 mg/kg (10 days) tapered by 4 mg every 2 weeks</td>
<td>CR five patients at median 3 months (one relapse at 5 months); PR seven patients</td>
<td>BCD: 9/10 Anti-DNA ↓ C3/C4 ↑</td>
</tr>
<tr>
<td>Leandro et al.</td>
<td>24</td>
<td>SLE</td>
<td>RTX 500 mg or 1 g ×2 (2 weeks apart) plus CTX 750 mg ×2 (2 weeks apart) plus CS 60 mg, 5 days or MP ×2 (2 weeks apart) or continued AZA</td>
<td>BILAG (13.9/5.0 (6 months))</td>
<td>BCD: 23/24 Anti-DNA ↓ C3 ↑</td>
</tr>
<tr>
<td>Vigna-Perez et al.</td>
<td>22</td>
<td>SLE and class III/IV LN</td>
<td>RTX 500 mg or 1 g ×2 (2 weeks apart) plus baseline ISP</td>
<td>MEX SLEDAI (10.8/6.8 (3 months)); CR five patients; PR seven patients; improvement in ≥1 renal parameter six patients</td>
<td>BCD: 20/22 Anti-DNA ↔ C3/C4 ↔</td>
</tr>
<tr>
<td>Gunnarson et al.</td>
<td>7</td>
<td>SLE and class III/IV LN</td>
<td>RTX 375 mg/m² ×4 (weekly) plus CTX 0.5 mg/m², ×2 (4 weeks apart) plus MP/HC, ×4 weekly plus CS 1 mg/kg (1 week then tapered)</td>
<td>SLEDAI (15/3); CR three patients; PR one patient; (at 6 months) WHO class transformation in all responders</td>
<td>BCD: 5/6 Anti-DNA ↓ C1q ab ↓ C3/C4 ↑</td>
</tr>
</tbody>
</table>

Adapted from Favas and Isenberg.³

AZA, azathioprine; BCD, B cell depletion; BILAG, British Isles Lupus Assessment Group; CR, complete remission; CS, corticosteroids; CTX, cyclophosphamide; HC, hydrocortisone; LN, lupus nephritis; MP, methylprednisolone; PR, partial remission; RTX, rituximab; SLAM, Systemic Lupus Activity Measure; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; WHO, World Health Organization.
Rituximab as induction therapy

The use of RTX as induction therapy in LN has recently been established by Pepper et al.\textsuperscript{25} They devised a standard treatment protocol comprising RTX induction therapy and maintenance with MMF for patients treated with CS with biopsy-proven LN class III, IV and V. Induction therapy consisted of two doses of RTX at days 1 and 15 with variable addition of intravenous MP. MMF maintenance was initiated at 1 g/day and titrated according to mycophenolate acid levels. At 12 months, 6/18 (33\%) attained CR and 6/18 (33\%) PR. Two patients achieved PR by 9 months but relapsed by 12 months. Four patients did not respond. At 12 months, four patients had stopped CS and a further two stopped by 24 months. Six patients were maintained on a lower dose of CS (reduced from a mean of 12 mg to 6 mg at 1 year), suggesting an important role for RTX as a steroid-sparing agent.

B cell depletion

The degree and duration of B cell depletion (BCD, <5 CD19+ B cells per μl) usually correlates with improvement in disease activity and scores,\textsuperscript{3} and BCD has been shown to be related to peak serum concentration achieved.\textsuperscript{20} Differences in dosing regimen, for example low-dose versus high-dose RTX or 375 mg/m\textsuperscript{2} of body surface area ×4 protocol compared with the 1000 mg ×2 with a 2-week interval has not demonstrated any significant clinical advantages.\textsuperscript{3,20} However, it has been suggested that using a smaller dose of RTX may predispose to the development of human anti-chimeric antibodies (HACA).\textsuperscript{21} A clinical response appears to be absent in a select group of patients. Some non-responders show polymorphisms of the CD64 (Fc\textgamma RI) gene leading to a phenotype with a low affinity for RTX.\textsuperscript{26} Failure to deplete, earlier repopulation and the presence of high-titre HACA antibodies has also been shown to be more common in Afro Caribbean people, and failure to deplete correlates with disease relapse.\textsuperscript{3,20} These findings are of significant clinical relevance as LN in Afro Caribbean people is often more aggressive and refractory.

Anti CD22: epratuzumab

CD22 is a 135 kDa glycoprotein member of a class of adhesion molecules that regulates B cell activation and interaction with T cells.\textsuperscript{27} CD22 is expressed in the cytoplasm of pro B and pre B cells and on the surface of mature cells. Like CD20 it is not expressed on plasma cells. Epratuzumab (EPZ) is a recombinant humanized monoclonal immunoglobulin G antibody to CD22 antigen. Its effect is mediated by antibody-dependent cellular cytotoxicity \textit{in vitro} and may also exhibit B cell receptor function.\textsuperscript{28} Dorner et al. reported a phase II open labelled trial of EPZ in 14 patients with moderately active SLE. Patients received 360 mg/m\textsuperscript{2} EPZ every 2 weeks for 4 weeks. A statistically significant improvement in BILAG was observed at 6, 10 and 18 weeks follow-up. Seventy-seven per cent showed a ≥50\% improvement at 6 weeks. Four patients exhibited renal manifestations at baseline (typically mild/stable proteinuria, three of four (75\%) had an improvement from baseline BILAG categorical score. One patient, however, manifested deterioration of proteinuria at 10 weeks.\textsuperscript{29}

In August 2009, UCB-Immunomedics announced exciting results on a 12-week dose and regimen-ranging study comparing EPZ with placebo in patients with SLE.
A clinically meaningful treatment effect of EPZ over placebo in SLE patients was found. The 227 patients in the study had moderate to severely active disease in multiple systems and the primary efficacy measure was a combined index end-point. Treatment advantage of EPZ over placebo reached 24.9% at week 12.\textsuperscript{30}

**Anti-BlyS: belumimab**

B lymphocyte stimulator (BLyS) is a factor determining the survival of B cells. BLyS binds to BAFF receptor (BAFFR) and BlyS receptor 3 expressed on human immature transitional naïve germinal centre and memory B cells, which determines the survival of these cells, activates IgM+IgD+ B cells to class switch and co-stimulates proliferation and cytokine secretion by T cells.\textsuperscript{31} Overexpression of BlyS in murine models leads to manifestations of anti-dsDNA antibodies, rheumatoid factor immune complexes and glomerulonephritis.\textsuperscript{32}

Wallace et al. reported on a phase II trial of 449 patients with active SLE randomized to receive belumimab (BEL) (1, 4 or 10 mg/kg) or placebo on day 0, 14 and 28 and then every 4 weeks for 76 weeks. Placebo patients were later switched to BEL. Over 52 weeks, BEL did not reach its primary end-point of reducing the clinical signs and symptoms of SLE as measured by the Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) and SLEDAI (SS), but BEL delayed flare onset after 6 months. Surprisingly, nearly 30% of patients in this study were ANA negative raising concerns about the diagnosis of the patients being treated. However, in the sero-positive population (ANA >1/80, anti-dsDNA ≥30 IU), BEL significantly reduced SS and BILAG scores across five of eight systems. Circulating B cells were reduced by 54–70% and C4 increased by 33% by week 52, and 15% of patients positive for anti-dsDNA sero-converted to negative compared with 3% on placebo.\textsuperscript{22,33}

In October 2009, Human Genome Sciences and GlaxoSmithKline announced positive phase III study results for BEL in SLE. The BLISS-52 multi-centre, randomized double blinded placebo controlled trial randomized 865 patients with active SLE (SS >6 and serologically active SLE (ANA ≥1/80 and or anti dsDNA ≥30) to receive placebo plus standard treatment of care (ST), BEL 1 mg/kg/ST or BEL 10 mg/kg/ST. The primary efficacy end-point or SLE responder index (SRI) at week 52 was a ≥4 point improvement in SS and no new BILAG 1A or 2B organ domain flares and no worsening in physician’s global assessment (PGA). Based on intention to treat analysis, BEL met its primary efficacy end-point of superiority versus placebo at 52 weeks. Statistically significant improvements were shown for BEL/ST of 57.6% for 10 mg/kg BEL and 51.7% for 1mg/kg BEL, respectively, versus placebo/ST.

The number of patients who reduced their prednisolone dose to 7.5 mg/day or less was significantly higher in the 1 mg/kg group compared with placebo/ST (20.6% versus 12%, p=0.025). Significantly fewer patients in the BEL/ST 10 mg/kg group increased their prednisolone to greater than 7.5 mg/day (19.8% versus 35.8%, p=0.02), or developed new BILAG 1A or 2B flares (18.6% versus 30%, p=0.0036). The time to first flare was also significantly longer in both BEL/ST groups. Overall rates of serious adverse events and infections were comparable to placebo/ST.\textsuperscript{*34}

The results of a second phase III superiority trial (BLISS-76) evaluating the efficacy and safety of BEL in 865 North American patients with SLE has also recently been
reported to have met its primary superiority end-point. A statistically significant improvement was shown in patient response rate for BEL/ST 10 mg/kg versus placebo/ST as measured by the SRI at week 52 (43.2% for 10 mg/kg BEL versus 33.8% placebo, p=0.021). The BEL 1 mg/kg group did not achieve a statistically significant improvement (40.6% for 1 mg/kg BEL versus 33.8% placebo, p=0.10).^35

**Blockade of co-stimulatory molecules**

**CTLA4-IG**

The interaction of B7 on B cells and CD28 on T cells provides an important second co-stimulatory signal for T cell activation and production of antibodies by B cells. Cytotoxic T lymphocyte antigen (CTLA4) is expressed only on activated T cells and this interaction leads to negative inhibition of T cells. A fusion protein consisting of CTLA4 and an immunoglobulin chain (CTLA4-Ig) binds B7 with a higher affinity than CD28 and hence inhibits the B7/CD28 interaction.^36

Merrill et al. carried out a 12-month exploratory study on the efficacy and safety of abatacept (CTLA4-Ig) in SLE. Two-hundred and ninety-three patients with SLE and active polyarthritis, serositis or discoid lesions were randomized 2:1 to receive abatacept (∼10 mg/kg) or placebo by IV infusion on days 1, 15, 29 then every 4 weeks. Prednisone (30 mg/day or equivalent) was given for 1 month then tapered according to protocol. The primary end-point was the proportion of patients with new SLE flare (adjudicated BILAG A or B) after the start of steroid taper over 1 year; however, there was no superiority of abatacept over placebo. Results for secondary BILAG end-points were similar.^37

The ACCESS (Abatacept and Cyclophosphamide Combination Therapy for Lupus Nephritis) trial, which is examining whether the addition of abatacept (a formulation of CTLA4-Ig) to standard therapy with CTX therapy is more effective in improving LN than CTX alone, is currently under way.

**CD40: CD40 ligand blockade**

The CD40: CD40 ligand interaction between B and T cells is also an important co-stimulatory signal for lymphocyte proliferation and activation.^38 Selective blockade of CD40/CD40L with BG9588, a humanized monoclonal antibody to CD154/CD40 ligand, has been shown in a small open labelled study of 28 patients with active proliferative LN to improve titres of anti-dsDNA and reduce proteinuria by 50%. However, the trial was terminated early due to an increased incidence of thrombo-embolic events.^39

**Future directions**

The prognosis of patients with LN has improved dramatically over the past few decades and the development and use of targeted therapy may be associated with higher efficacy and lower toxicity. Potential future treatments for SLE and LN include blockade of BlyS/APRIL (A PRoliferation-Inducing Ligand) heterodimers, which have BlyS-like activity with TACI (transmembrane activator and calcium-modulator and cytophilin ligand interactor)-Ig.^40,41 Atacicept a soluble form of TACI and a
recombinant fusion protein that blocks both BlyS and APRIL activity has been shown to have efficacy in small numbers of SLE patients.\textsuperscript{42,43} However, phase II trials of atacicept in the treatment of LN were halted due to an observed increased incidence of serious infections in the treatment group, which was linked to a notable drop in total immunoglobulin levels, although this occurred in association with MMF given prior to the infections.

Rontalizumab (RNZ) an anti-interferon (IFN) $\alpha$ monoclonal antibody has also recently been evaluated as a potential treatment for SLE. Elevated mRNA levels of IFN-regulated genes (IRGs) have been identified in the peripheral blood of the majority of SLE patients and are thought to be associated with disease pathogenesis. McBride et al. assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of RNZ in a phase I dose-escalation study in adults with mild to moderate SLE. They showed a decline in expression level of seven IRGs in the majority of patients after dosing with 3 mg/kg and 10 mg/kg intravenous RNZ, which was sustained for 1 month following single and repeated dosing. This was consistent with the expected down-modulation of the IFN signalling pathway, suggesting the possibility of clinical benefit in SLE.\textsuperscript{44} A follow up phase II study by Gentech is currently under way.

Tociluzumab (TCZ), a humanized anti-interleukin 6 (IL-6) receptor monoclonal antibody has also been evaluated in the treatment of SLE. In an open label phase I dose-escalation study, 16 patients with mild to moderate SLE were randomized to receive differing doses of TCZ (2 mg/kg, 4 mg/kg and 8 mg/kg) intravenously every other week for 12 weeks. Decreases in the absolute neutrophil count were seen in the 4 mg/kg and 8 mg/kg groups. There was a significant improvement in the SS in eight of 15 patients. Arthritis improved or resolved in all patients with arthritis at baseline, and levels of anti-dsDNA antibodies decreased by a median of 47% in patients in the 4 mg/kg and 8 mg/kg dosage groups, with a 7.8% decrease in their IgG levels. These changes, together with a significant decrease in the frequency of circulating plasma cells, suggested a specific effect of TCZ on autoantibody-producing cells.\textsuperscript{45}

Other biological agents in the preliminary phase of development include the anti-complement (C5) monoclonal antibody,\textsuperscript{46} and anti-IL-10 monoclonal antibody.\textsuperscript{47}

**Take home points**

1. Over the last few years, treatment of SLE and LN has moved from serendipity to immunological sense focusing on biological agents that target the cells and molecules specifically involved in the critical pathways in SLE pathogenesis.
2. Biological agents offer the possibility of efficacious and safe treatment options for patients with refractory disease, reducing the burden of immunosuppressive drugs.
3. In spite of some recent disappointing results with biological, including abatacept and rituximab, a number of newer agents have shown encouraging benefits.
4. Belumimab and epratuzumab have both met their primary end-points in the BLISS-52, BLISS-76 and epratuzumab phase IIb trials, and rontalizumab and tociluzumab have shown promising results in phase I studies.
References and recommended reading

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest


30. UCB and Immunomedics. (2009) UCB and Immunomedics announce positive results for epratuzumab phase Ib study in systemic lupus erythematosus (SLE), [UCB. com], press release, August.


35. *Benlysta (belimumab) 10 mg/kg plus standard of care met its primary efficacy endpoint by achieving a statistically significant improvement in patient response rate versus placebo plus standard of care at week 52 in BLISS-76 [GSK.com], Press statement, November 2009.*


Chapter 7

Systemic lupus erythematosus (SLE) in pregnancy

Aisha Lateef and M. Petri

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects young females of childbearing age. Fertility is generally conserved in SLE, unless the woman has been treated with cyclophosphamide. Improvement in survival and quality of life in SLE patients has led to an increased number of pregnancies observed during the course of the disease.

Pregnancies in SLE are associated with important maternal and foetal morbidity. In a recent US study of 16.7 million pregnancies, 13555 occurred in SLE patients with an increased maternal mortality of more than 20-fold. The odds ratio was 1.7 for Caesarean section, 2.4 for pre-term labour and 3.0 for pre-eclampsia. Published data have identified several risk factors for poor pregnancy outcomes, including hypertension, anti-phospholipid (aPL) syndrome and active disease. In addition, several studies have suggested that renal involvement, especially the presence of active lupus nephritis (LN) at the time of conception may contribute to adverse maternal and foetal outcomes. SLE can present for the first time during pregnancy and patients with established non-renal SLE can develop the first episode of nephritis during pregnancy. Treatment of LN, either established or new onset, remains problematic in pregnancy and coordinated multi-disciplinary care is required to optimize outcomes.

Physiological renal changes in pregnancy pertinent to SLE

The kidneys undergo profound haemodynamic changes during normal pregnancy. Renal plasma flow rises from early in pregnancy, and by the second trimester has increased by 60–80%. It then falls throughout the third trimester, but at term is still 50% greater than pre-pregnancy values. Concomitantly, the glomerular filtration rate (GFR) also increases by almost 50% with a resultant fall in serum urea and creatinine levels. The increased GFR, reduced proximal reabsorption and alterations in the electrostatic charge of the glomerular filter lead to increased urinary excretion of protein, and levels of up to 300 mg/24 hours are considered within the normal range in pregnancy. During pregnancy, there is physiological sodium and water retention, with decreased ability to excrete a sodium and water load, especially near term, contributing to the oedema. There is also an increased risk of hydronephrosis secondary to pelvicalyceal dilatation. Important hormonal changes include increased levels of...
erythropoietin, renin and vitamin D to meet the increased demands of the growing foetus. These changes may create diagnostic and therapeutic challenges in patients with pre-existing renal disease such as LN. As an example, SLE patients may have increased proteinuria due to physiological changes, worsening of primary disease or withdrawal of medications (e.g. angiotensin converting enzyme (ACE) inhibitors). Patients with impaired renal function at conception will have impaired physiological adaptations, leading to an increased frequency of pregnancy complications, as discussed below.

**Lupus nephritis and pregnancy**

**Effect of pregnancy on renal SLE**

One of the major issues in SLE pregnancy is the risk of disease flare during pregnancy or post partum. Multiple studies have determined the risk of renal flare in patients with established LN to be between 10% and 69% during pregnancy (Table 7.1). The heterogeneity of study designs, different patient populations and variable control groups being used by different studies has likely led to wide variations in the reported risks. Maternal disease activity at conception has been identified as one of the strongest predictors of renal flares. This risk is reduced to less than half if SLE is in remission (defined as stable renal function, inactive urine sediment and proteinuria of <500 mg/day) for at least 6 months at the time of conception. A large multi-centre study of 113 pregnancies in 81 women with established biopsy-proven nephritis evaluated the predictors of poor outcomes. Renal flare rates were reported to be 14% if disease was in complete remission at conception, whereas the risk went up to 45–66% with active disease. Similarly, other studies have reported higher flare rates and worse outcomes in patients with evidence of active nephritis, reinforcing the need for planned pregnancies in SLE (Table 7.2).

Renal flares during pregnancy pose diagnostic and therapeutic problems for the physician. The measurement of parameters of renal disease is complicated by pregnancy. Oedema and proteinuria in pregnancy could be physiological as described or secondary to a lupus flare or pre-eclampsia. This makes diagnosis of renal flare difficult, although some clinical and laboratory parameters may help in the differentiation. Complement levels tend to increase in pregnancy, so a downward trend or low normal level may indicate lupus serological activity. Although not a very sensitive marker, an active urinary sediment, if present, can help in the diagnosis of renal lupus flare. Similarly, evidence of extra-renal systemic disease activity may aid in the differentiation. Lupus activity scales that are specific for pregnancy, (SLEPDAI, LAI-P) have been developed but mostly remain as a research tool. Physician’s global assessment has been used at the Hopkins Lupus Center with good internal agreement. Occasionally, renal biopsy during pregnancy has to be considered for definitive diagnosis and treatment.

Pregnancy may accelerate the decline in renal function in women with chronic renal impairment, depending on the baseline creatinine level and worsened by the presence of hypertension. Severe renal flares with progression to renal failure can occur, albeit less commonly, in women with normal renal function at conception. Disease activity during pregnancy poses special therapeutic problems as maternal treatment has
to be balanced against the risk of foetal toxicity. Mild disease activity can be treated with corticosteroids but they are associated with higher maternal morbidity, as discussed later.\textsuperscript{24} Moderate to severe disease activity may require addition of an immunosuppressant for disease control. Many of the drugs commonly used to treat LN (cyclophosphamide, mycophenolate mofetil, rituximab) cannot be used in pregnant patients.\textsuperscript{24} Azathioprine, cyclosporine and hydroxychloroquine have been safely used in pregnancy but may not be sufficient in severe disease. Intravenous immunoglobulin has been used but is fraught with multiple problems including fluid overload and nephrototoxicity.\textsuperscript{25–27} Hence, the management of established or new onset LN in pregnancy remains a challenge, despite the advances in SLE treatment.

### Table 7.1 Effect of pregnancy on lupus nephritis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study design</th>
<th>No. of women (pregnancies)</th>
<th>Renal flares (%)</th>
<th>Worsening of renal function (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagner et al.\textsuperscript{8}</td>
<td>2009</td>
<td>Chart review</td>
<td>58 (90)</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Carvalheiras et al.\textsuperscript{15}</td>
<td>2009</td>
<td>Retrospective cohort study</td>
<td>43 (51)</td>
<td>69</td>
<td>NA</td>
</tr>
<tr>
<td>Imbasciati et al.\textsuperscript{7}</td>
<td>2008</td>
<td>Prospective multi-centre study</td>
<td>81 (113)</td>
<td>30</td>
<td>2.7</td>
</tr>
<tr>
<td>Tandon et al.\textsuperscript{17}</td>
<td>2004</td>
<td>Prospective LN/non-pregnant SLE</td>
<td>53 (78)</td>
<td>44.6</td>
<td>17.3</td>
</tr>
<tr>
<td>Hernandez et al.\textsuperscript{4}</td>
<td>2002</td>
<td>Prospective cohort study</td>
<td>60 (103)</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Moroni et al.\textsuperscript{11}</td>
<td>2002</td>
<td>Retrospective New onset LN/established LN</td>
<td>48 (70)</td>
<td>18.9</td>
<td>7</td>
</tr>
<tr>
<td>Huong et al.\textsuperscript{6}</td>
<td>2001</td>
<td>Retrospective Planned/unplanned pregnancies</td>
<td>22 (32)</td>
<td>12.5</td>
<td>3</td>
</tr>
<tr>
<td>Petri et al.\textsuperscript{16}</td>
<td>1991</td>
<td>Prospective cohort study</td>
<td>37 (40)</td>
<td>43</td>
<td>NA</td>
</tr>
<tr>
<td>Jungers et al.\textsuperscript{10}</td>
<td>1982</td>
<td>Retrospective New onset LN/established LN</td>
<td>36 (104)</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td>Hayslett et al.\textsuperscript{9}</td>
<td>1980</td>
<td>Retrospective Questionnaire</td>
<td>47 (65)</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>Fine et al.\textsuperscript{14}</td>
<td>1981</td>
<td>Retrospective cohort study</td>
<td>39 (52)</td>
<td>23</td>
<td>9.6</td>
</tr>
</tbody>
</table>

LN, lupus nephritis; SLE, systemic lupus erythematosus.
Effect of renal disease on pregnancy

The outlook for SLE pregnancies has significantly improved over the last 35 years. The risk of foetal loss in one study was reported to be reduced from 43% before 1975 to 17% in 2000–2003. Other recent studies have also reported a rate of live birth of 83–90%, 2,7,15,19 These improved outcomes are likely to be the result of early recognition of poor predictors, and better rheumatological, obstetric and neonatal care. Despite these improvements, pregnancy in SLE is still associated with an increased risk of maternal and foetal complications, including miscarriage, intrauterine growth restriction (IUGR), intrauterine death (IUD), pre-term delivery (and the associated morbidity and mortality) and pre-eclampsia. The reported rates of foetal loss range from 9% to 53%, prematurity between 16% and 58% and IUGR between 5% and 35% (Table 7.3). 2,4,6–9,14,15,18,29

Foetal loss

Foetal loss in SLE pregnancy can occur in any trimester. Early losses are associated with aPL antibodies but also with high SLE disease at conception and renal involvement. Late losses are more strongly associated with aPL positivity. 2,3 A large study of 166 pregnancies from our Hopkins Lupus Pregnancy cohort identified the presence of proteinuria, aPL antibodies, thrombocytopenia and hypertension (PATH) to be associated with a many-fold increased risk of pregnancy loss. 3 Moroni et al., in a study of 70 pregnancies, reported similar results, with an odds ratio for pregnancy loss of 17.8 with aPL positivity, 13.3 with proteinuria and 6.4 with hypertension. 11 Active renal disease at the time of conception increases the risk of foetal loss in comparison with those patients who have either been treated to remission or do not have renal involvement, as reported in multiple studies (Table 7.3). 5,8,10 Another large study from the Hopkins cohort also addressed the issue of pregnancy outcomes in relation to disease activity and documented a threefold increase in pregnancy loss with high

Table 7.2 Disease activity at conception predicts the rate of renal flares

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>No. of women (pregnancies)</th>
<th>Disease activity</th>
<th>Flares (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imbasciati et al. 2</td>
<td>Prospective multi-centre study in women with known LN</td>
<td>81 (113)</td>
<td>Complete remission</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Partial remission</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Proteinuria</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nephrotic syndrome</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GFR&lt;60 (ml/min)</td>
<td>69</td>
</tr>
<tr>
<td>Moroni et al. 11</td>
<td>Retrospective</td>
<td>48 (70)</td>
<td>Active</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>New onset LN/established LN</td>
<td></td>
<td>Inactive</td>
<td>5</td>
</tr>
<tr>
<td>Jungers et al. 10</td>
<td>Retrospective</td>
<td>36 (104)</td>
<td>Active</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>New onset LN/established LN</td>
<td></td>
<td>Inactive</td>
<td>9</td>
</tr>
<tr>
<td>Hayslett et al. 9</td>
<td>Retrospective questionnaire</td>
<td>47 (65)</td>
<td>Active</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Remission</td>
<td>32</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; LN, lupus nephritis.
disease activity in the first and second trimesters. \(^2\) Imbasciati et al. also identified hypocompletenaemia, a surrogate marker of disease activity, to be the strongest predictor of poor pregnancy outcomes. \(^7\)

**Anti-phospholipid syndrome (APS) and pregnancy loss**

aPL antibodies are frequently present in SLE patients: estimates have ranged between 24% and 50%. \(^{30,31}\) APS is currently defined according to the revised Sapporo (Sydney) criteria, which require the presence of at least one clinical criterion of thrombosis and/or pregnancy morbidity with the persistence of medium to high titre anti-cardiolipin (aCL) antibodies, anti-\(\beta_2\) glycoprotein and/or the lupus anti coagulant (LAC) on at least two occasions, 12 weeks apart. \(^{32}\) The pregnancy morbidity can be either:

- recurrent (>3) first trimester losses (chromosomal/structural causes excluded);
- one late loss of a morphologically normal foetus;
- premature birth as a result of severe pre-eclampsia or placental insufficiency.

Management of patients with aPL positivity in SLE pregnancy depends on the presence or absence of other risk factors and can generally be divided into three groups.

### Table 7.3 Effect of SLE on foetal outcomes

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study objective</th>
<th>No. of women (pregnancy)</th>
<th>Pregnancy loss (%)</th>
<th>Prematurity (%)</th>
<th>IUGR (%)</th>
<th>Live full-term deliveries (%)</th>
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</thead>
<tbody>
<tr>
<td>Wagner et al.(^8)</td>
<td>Outcomes in active versus inactive LN</td>
<td>58 (90)</td>
<td>Active 35</td>
<td>52</td>
<td>4</td>
<td>9</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Quiescent 25</td>
<td>30</td>
<td>5</td>
<td>45</td>
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<td></td>
<td></td>
<td></td>
<td>No LN 9</td>
<td>19</td>
<td>4</td>
<td>64</td>
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<tr>
<td>Carvalheiras et al.(^15)</td>
<td>Outcomes in SLE pregnancy</td>
<td>43 (51)</td>
<td>10</td>
<td>16</td>
<td>NA</td>
<td>74</td>
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<tr>
<td>Imbasciati et al.(^7)</td>
<td>Outcomes in LN pregnancy</td>
<td>81 (113)</td>
<td>13</td>
<td>31</td>
<td>24</td>
<td>91</td>
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<tr>
<td>Hernandez et al.(^4)</td>
<td>Outcome predictors in SLE pregnancy</td>
<td>60 (103)</td>
<td>36</td>
<td>28</td>
<td>35</td>
<td>66</td>
</tr>
<tr>
<td>Moroni et al.(^11)</td>
<td>Outcomes in LN pregnancy</td>
<td>48 (70)</td>
<td>36</td>
<td>20</td>
<td>5</td>
<td>64</td>
</tr>
<tr>
<td>Huong et al.(^6)</td>
<td>Outcomes in LN pregnancy</td>
<td>22 (32)</td>
<td>Planned 20</td>
<td>53</td>
<td>NA</td>
<td>24</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Unplanned 53</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clowse et al.(^2)</td>
<td>Effect of disease activity on outcomes</td>
<td>203 (267)</td>
<td>H activity 16</td>
<td>49</td>
<td>30</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>L activity 5</td>
<td>26</td>
<td>21</td>
<td>88</td>
</tr>
<tr>
<td>Jungers et al.(^10)</td>
<td>Outcomes in LN pregnancy</td>
<td>36 (104)</td>
<td>Active 43</td>
<td>11</td>
<td>NA</td>
<td>57</td>
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<td></td>
<td></td>
<td></td>
<td>Inactive 17</td>
<td>8.5</td>
<td></td>
<td>82</td>
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<tr>
<td>Fine et al.(^14)</td>
<td>SLE pregnancy</td>
<td>44 (58)</td>
<td>22.4</td>
<td>24</td>
<td>3</td>
<td>18</td>
</tr>
</tbody>
</table>

H, high; L, low; LN, lupus nephritis; NA, not available; SLE, systemic lupus erythematosus.
Low-risk patients are those with positive aPL and no prior pregnancy loss or history of thrombosis. The current consensus is to treat them with low-dose aspirin throughout the pregnancy. The second group comprises patients with recurrent early or one or more late foetal losses in presence of aPL. Current treatment recommendations include prophylactic-dose heparin with low-dose aspirin. The third group includes patients with thrombosis, who require full dose anticoagulation with heparin. Warfarin is contraindicated in pregnancy because of its teratogenic potential. Some women continue to miscarry in spite of treatment with heparin and aspirin. No set regimen exists for this clinical scenario; intravenous immunoglobulin or plasmapheresis has been used in open label studies but controlled studies have been negative.

**Pre-term birth**

Pre-term birth is the most common complication of SLE pregnancy with up to a third of pregnancies ending in delivery before 37 weeks, in contrast to 7% of pregnancies in healthy women. Several studies have attempted to identify the risk factors for increased risk with conflicting results. aPL antibody positivity was identified as a risk factor for pre-term birth in some studies but the association was not supported in other reports. The presence of proteinuria, maternal hypertension and use of prednisolone has been reported to be predictive of pre-term birth in some studies. High disease activity at the time of conception has emerged as the strongest predictor, whether measured clinically or serologically. The Hopkins Lupus Center database, including more than 300 SLE pregnancies, has identified a combination of two factors: high clinical activity and serologic activity, as the best way to predict pre-term birth. Our group analyzed the causes of pre-term birth and noted an association with premature rupture of membranes in 39% of cases. Other causes for pre-term birth include pre-eclampsia, HELLP syndrome, oligohydroamnios and foetal distress.

**Pre-eclampsia**

The risk of pre-eclampsia is higher in SLE pregnancies, occurring in 22–30% of pregnancies, compared with 5–7% in healthy pregnancies. Studies have suggested renal disease, thrombocytopenia and APS to be the predictors of pre-eclampsia in SLE. Differentiation between renal flare and pre-eclampsia is also complex, because both can present with increasing proteinuria, hypertension, thrombocytopenia and deterioration in renal function. However, hypocompletenaemia, active urine sediment or evidence of disease activity in other organs would point to a SLE flare. Studies have demonstrated that abnormal uterine blood flow correlates with an increased risk of pre-eclampsia and may also be useful as a diagnostic adjunct in SLE pregnancies. The measurement of new biomarkers for pre-eclampsia such as vascular endothelial growth factor receptor (sFlt-1) or placental growth factor (PlGF) await further evaluation. However, it is quite possible for the patient to have concurrent active LN and pre-eclampsia. Only delivery may help to provide a definitive answer.

**Renal function impairment**

In the presence of pre-existing renal disease, the degree of renal impairment is the major determinant of pregnancy outcome. Women with chronic kidney disease are
less able to make the renal adaptations needed for a healthy pregnancy, leading to an increased risk of both maternal and foetal complications during pregnancy. Foetal survival of pregnant women with mild or moderate renal disease is only slightly diminished, and irreversible deterioration of maternal renal function is uncommon. However, foetal outcome is particularly reserved with severe disease, when the perinatal mortality rate is approximately four times higher compared with mild or moderate disease.\textsuperscript{12,42} The rate of perinatal morbidity as a consequence of low birth weight or prematurity doubles from mild to moderate renal insufficiency from any cause and again from moderate to severe disease.\textsuperscript{43} In SLE patients on regular dialysis the success rate of pregnancy is less than 50%.\textsuperscript{18} In contrast, in women with SLE who have had a kidney transplant the outcome of pregnancy is good and comparable with that of renal transplant recipients with other primary renal disease.\textsuperscript{44}

### Management of pregnancy in SLE

#### Timing of pregnancy

Ideally, SLE pregnancies should be planned and disease should be under good control for at least 6 months prior to conception, as lupus activity at conception is a known predictor of adverse outcomes. This means that patients with active SLE should avoid pregnancy, highlighting the importance of contraception in SLE. Recommending a contraceptive method to women with systemic lupus may be difficult. Barrier- or behaviour-based methods have a high failure rate and their use alone may not be sufficient. For decades, oral contraceptives were withheld from women with SLE because of concerns of inducing or worsening disease activity. These concerns were based on early retrospective studies and animal data showing oestrogens to exacerbate the disease and hypoestrogenaemic states to be protective.\textsuperscript{45} A further concern was that up to 50% of patients with SLE may have aPL antibodies; the use of oral contraceptives in a hypercoagulable patient might be the ‘second hit’ leading to thrombosis.\textsuperscript{19} On the other hand, use of oral contraceptives might be beneficial in SLE patients beyond providing efficient contraception. Their use may preserve ovarian function in patients being treated with cyclophosphamide, prevent bone loss and osteoporosis, and prevent cyclical disease activity. Two large trials, by Petri et al. (SELENA-OC) and Sanchez-Guerrero et al., have addressed the issue of safety of oral contraceptives in SLE. There was no increase in flares, disease activity or adverse events with use of exogenous hormones in SLE.\textsuperscript{46,47} Although showing the safety of oral contraceptives in SLE, the results should be interpreted with caution. SLE patients with severely active disease were excluded in both trials. Patients with the LAC or medium to high titre aCLs were excluded from the SELENA-OC trial. The use of the progestin-only pill and intrauterine contraceptive device was also evaluated in the study by Sanchez-Guerrero et al., showing similar efficacy and safety as oral contraceptives.

#### Pre-conception assessment

One of the most important points in managing pregnancy in women with SLE is preconception assessment, evaluating the disease activity, gathering pertinent information
to estimate maternal and foetal risk and planning antenatal care. A comprehensive assessment of disease activity, organ involvement and damage as well as past obstetric history should be done. Disease activity at the time of conception is associated with poor outcomes and a previous complicated pregnancy is, by itself, an important adverse prognostic variable. Chronic renal failure, severe pulmonary hypertension, restrictive pulmonary disease and severe cardiac disease may significantly increase the maternal risk and may justify advice against pregnancy in such situations. A complete set of auto-antibodies should also be obtained, especially aPL, both aCL antibodies and LAC, which predispose to miscarriage and intrauterine foetal death. Anti-Ro and anti-La antibodies, if present, predispose to neonatal lupus including congenital heart block. SLE pregnancies should be treated as high-risk pregnancies. Close monitoring with coordinated care by rheumatologists, obstetricians and nephrologists (if indicated) is necessary for optimal outcomes.20

Pharmacological therapy during pregnancy

One of the critical issues in SLE pregnancy is the use of appropriate medications to treat the mother and not to compromise the safety of the baby at the same time. Pregnant women are excluded from drug trials so almost all safety information in pregnancy comes either from animal studies, inadvertent exposure during pregnancy or case reports. A recent consensus document has established, after an extensive literature review, the safety of a number of drugs commonly used in pregnant women with rheumatic diseases.48

Non-steroidal anti-inflammatory drugs (NSAIDS) are generally considered safe during the first and second trimesters. Several population-based cohort and case–control studies, including thousands of pregnancies, have documented no increased risk of congenital malformations from first trimester exposure.49,50 However, they should be avoided in the last weeks of pregnancy due to the risk of premature closure of the ductus arteriosus, estimated to be raised by 15-fold in a recent meta-analysis.51 Impaired foetal urine output, oligohydroamnios and even renal failure have been described in some open label studies, when NSAIDS were used as a tocolytic agent.52

Corticosteroids (except fluorinated compounds – dexamethasone and betamethasone) are largely inactivated by placental hydroxylases, thereby limiting foetal exposure and toxicity. Despite this, they can still cause important medical and obstetric problems, including diabetes, hypertension, pre-eclampsia and premature rupture of membranes, especially at higher doses. Experts have recommended use of the lowest possible dose, preferably below 20 mg/day and use of stress doses at delivery in patients on long-term corticosteroids. In cases of severe activity, intravenous pulses of 250–1000 mg of methylprednisolone can be used safely.19,48

The anti-malarial hydroxychloroquine is frequently prescribed to SLE patients. Studies have shown that it can prevent disease activity and damage accrual. Its discontinuation leads to flare in the majority of patients.53–55 The safety of hydroxychloroquine in pregnancy has been documented by multiple studies including hundreds of lupus pregnancies. A large cohort study of 257 pregnancies from the Petri lupus cohort and a randomized control trial by Levy et al. documented decreased disease activity and better outcomes in patients continuing hydroxychloroquine during pregnancy with no increase in adverse events or congenital malformations.56,57 A recent review of
all published data also concluded that hydroxychloroquine is safe during pregnancy. The international working group on medications during pregnancy also recommended continuing hydroxychloroquine treatment during pregnancy.

Most immunosuppressive drugs (cyclophosphamide, methotrexate, mycophenolate, leflunomide) are contraindicated during pregnancy (Table 7.4). The exceptions are azathioprine, cyclosporine and tacrolimus, all with an extensive experience in pregnant women, particularly in transplant recipients. There are very limited data on the B cell-depleting antibody, rituximab, during pregnancy. The current recommendation is to discontinue it before pregnancy.

Anti-hypertensive drugs are frequently needed in pregnant women with SLE. Some of the most common drugs in this group are contraindicated during pregnancy. Angiotension converting enzyme (ACE) inhibitors can cause affect foetal renal vascular tone leading to foetal kidney dysplasia and malfunction. This may cause foetal renal dysfunction and oligohydroamnios, leading to ACE inhibitor fetopathy with intrauterine growth retardation, hypocalvaria, limb deformities, pulmonary hypoplasia, marked foetal and neonatal arterial hypotension, renal failure and death.

Because of their similar mechanism of action, angiotensin II receptor blockers are also

Table 7.4 Pharmacotherapy during pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Permitted</th>
<th>Contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Prednisolone/Pulse methyl prednisolone</td>
<td>Betamethasone/dexamethasone (single course)</td>
</tr>
<tr>
<td>Anti-malarials</td>
<td>Hydroxychloroquine</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressives</td>
<td>Azathioprine</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leflunomide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rituximab</td>
</tr>
<tr>
<td>Anti-platelets</td>
<td>Aspirin</td>
<td>Ticlopidine</td>
</tr>
<tr>
<td></td>
<td>Dipyrimidole</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Anti coagulants</td>
<td>Heparin</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Anti-hypertensives</td>
<td>Methyldopa</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td></td>
<td>Labetalol</td>
<td>ARBs</td>
</tr>
<tr>
<td></td>
<td>Hydralazine (caution)</td>
<td>Diuretics</td>
</tr>
<tr>
<td></td>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td>Analgesics and anti-</td>
<td>Acetaminophen</td>
<td>COX II inhibitors</td>
</tr>
<tr>
<td>inflammatory drugs</td>
<td>NSAIDS (till week 32)</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis prevention/treatment</td>
<td>Calcium supplements</td>
<td>Bisphosphonates</td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
<td></td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; COX, cyclooxygenase; NSAID, non-steroidal anti-inflammatory drug.
contraindicated during pregnancy. Thus, treatment of hypertension during pregnancy is limited to older agents, such as methyldopa, hydralazine and labetalol. If the patient does not respond to therapy with the preferred agents or cannot tolerate such therapy because of adverse drug reactions, second-line agents can be considered. Nifedipine has been used in pregnant patients without any reports of teratogenicity. ß-blockers remain a possible choice, although they have been associated with IUGR, foetal bradycardia and may potentially worsen Raynaud’s phenomena in SLE patients. Diuretics can be used, if required for fluid balance in renal impairment or in combination with other anti-hypertensives in refractory cases. Studies including thousands of pregnancies did not find any increased teratogenicity, but concerns remain about maternal volume depletion and reduced uteroplacental perfusion. 62, 63

Low-dose aspirin is frequently used in SLE patients with aPL positivity or other cardiovascular risk factors and should be continued during pregnancy. A meta-analysis of aspirin use in high-risk pregnancies documented a significantly reduced risk of pre-term delivery with no increase in adverse events. 64 Among alternative anti-platelet agents, dipyrimadole is considered safe. There are very limited data on newer agents, such as clopidogrel. Hence they should be avoided in pregnancy. Heparin is used in addition to aspirin to treat the pregnancy morbidity in APS pregnancies and has improved the outcome of such pregnancies significantly. 33, 65 It does not cross the placenta and can be safely used in pregnancy. Warfarin must be avoided during organogenesis (weeks 6–10) due to the well-defined warfarin embryopathy syndrome. 66 There are very limited data on newer anti coagulants like fondoparinux and ximegalatran, and they should be avoided in pregnancy. 48 Women receiving heparin during pregnancy, as well as those treated with corticosteroids should receive calcium plus vitamin D until the end of lactation. Bisphosphonates accumulate in bone for long periods. There are animal data of foetal bone toxicity with bisphosphonate exposure during pregnancy and very limited human experience. Current recommendation is to avoid pregnancy for at least 6 months after discontinuation of bisphosphonates. 48 Thus, the armamentarium to treat SLE is limited during pregnancy (Table 7.4). Proper planning, judicious use of medications and close monitoring is vital for a successful outcome.

Take home points

1. Pregnancy in SLE is associated with increased maternal and foetal morbidity including disease flares, foetal loss, prematurity, IUGR and pre-eclampsia.
2. Disease flares are more common during pregnancy.
3. Disease activity at the time of conception is associated with poor outcomes.
4. Pre-conception assessment is necessary to risk-stratify the patients.
5. Differentiation between renal flares and pre-eclampsia may be difficult in some cases.
6. Pre-term births are frequent in SLE pregnancies. The combination of highly active clinical lupus and abnormal serological tests (low complement, high anti-dsDNA) is most predictive of pre-term birth.
7. Pharmacotherapy during pregnancy needs to be adjusted for the safety of the mother and foetus.
References

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest


*Summarizes the important clinical issues in management of SLE pregnancies.*
   *Comprehensive evidence-based review of management of SLE pregnancy.
   **Excellent evidence-based review of current management of APS pregnancies.


**Provides guidelines for use of anti-inflammatory and immunosuppressive drugs in pregnancy, based on extensive review of literature and expert consensus.**


*Summarizes all the evidence for use of hydroxychloroquine in pregnancy.


*Important updates from literature on use of biological agents during pregnancy.


**Excellent review of literature with recommendations for management of recurrent pregnancy losses in aPL-positive patients.

Chapter 8

Renal involvement in the anti-phospholipid syndrome

Joyce Rauch and Jerrold S. Levine

Introduction

Anti-phospholipid antibodies (aPL) are a heterogeneous group of autoantibodies that recognize various combinations of phospholipids and/or phospholipid-binding proteins. ‘Anti-phospholipid syndrome’ (APS) is a term that was first coined in the mid-1980s to describe the association of aPL with a syndrome of hypercoagulability. Despite the prominence and variety of renal manifestations in this syndrome, initial descriptions of APS did not include the kidney among the many organ systems affected by this disease. Although there has been growing interest in the effects of APS on the kidney, the full range of renal manifestations, in particular those related to chronic effects of APS, may still be underestimated. In this review, we focus on basic principles and recent advances in our understanding of APS. A more detailed discussion of APS in general, and its renal manifestations in particular, as well as a more complete list of references, may be found in several earlier reviews.1,2

Terminology and basic properties of aPL

The nomenclature for aPL is historically based and can be very confusing. aPL is a general term for autoantibodies that recognize phospholipids and/or phospholipid-binding proteins. Categorization of aPL into subsets is based on the method of detection (cf. table 2 in1). aPL detected functionally, by their ability to prolong clotting times in an in vitro coagulation assay, are referred to as lupus anticoagulants (LAC). In contrast, aPL detected immunologically, by their ability to bind to plastic surfaces coated with either cardiolipin (CL) (a phospholipid) or \( \beta_2 \) -glycoprotein I (\( \beta_2 \) GPI) (a phospholipid-binding protein), are called anti-cardiolipin antibodies (aCL) or anti-\( \beta_2 \) GPI antibodies (anti-\( \beta_2 \) GPI), respectively.

aPL can occur in association with a broad range of diseases and physiological conditions, including maintenance haemodialysis, but the two most important associations are with autoimmune diseases, especially systemic lupus erythematosus (SLE), and infectious diseases like syphilis. Despite their name, aPL found in the setting of autoimmune diseases are most often directed against a phospholipid-binding protein (alone or complexed to phospholipid) rather than against phospholipid alone. LAC is the classic example of aPL associated with autoimmunity. In contrast, aPL in the setting of
infectious diseases usually recognize phospholipid alone, but not the phospholipid-protein complex. For example, antibodies detected by the VDRL (Venereal Disease Research Laboratory) serological assay for syphilis bind to CL alone, and their binding is inhibited, rather than enhanced, by phospholipid-binding proteins, like β₂GPI, which compete with VDRL antibodies for binding to CL. Another important distinction between aPL occurring in infection versus autoimmune diseases is their health-related consequences. In general, aPL associated with infectious diseases lack a clinically important impact on coagulation. We will therefore focus exclusively on aPL occurring in association with autoimmunity.

Despite the frequent overlap between LAC and either aCL or anti-β₂GPI, these antibodies are not necessarily identical. Some patients have LAC, without detectable aCL or anti-β₂GPI, most likely because the aPL of these patients react with phospholipids other than CL or phospholipid-binding proteins other than β₂GPI (e.g., prothrombin, protein C, protein S, annexin V and several kininogens). Other patients have aCL and/or anti-β₂GPI that possess no discernible LAC activity, probably because they do not recognize phospholipid-binding protein/phospholipid complexes involved in \textit{in vitro} coagulation assays.

The choice of CL as the phospholipid in immunological assays for aPL was based on the historical observation that patients with SLE often had false-positive VDRL assays, in which CL is the antigen. However, the reactivity of aPL is, in general, unaffected by substitution of CL with another negatively charged (anionic) phospholipid, such as phosphatidylserine. In marked contrast, substitution of CL with a net neutrally charged phospholipid, such as phosphatidylethanolamine, virtually eliminates reactivity. The basis for this preference lies in the phospholipid-binding proteins themselves (e.g., β₂GPI), which interact strongly with anionic phospholipids, but weakly if at all with net neutrally charged phospholipids. In conjunction with negatively charged phospholipid, β₂GPI and other phospholipid-binding proteins comprise the antigenic targets of most aPL.

Paradoxically, in terms of their name, LAC are associated with thrombo-embolic events, and not with clinical bleeding. LAC can interfere with both anticoagulant and procoagulant pathways. Although the phospholipid surface and assay conditions in most \textit{in vitro} coagulation assays favour inhibition of procoagulant pathways, and therefore prolongation of clotting by LAC, the microenvironment of cell membranes \textit{in vivo} probably promotes inhibition of anticoagulant pathways by LAC, and therefore thrombosis.

The stimulus or antigen leading to aPL production remains unknown. It is presumed that the initial target of the autoimmune response is a cell surface complex between one of several phospholipid-binding proteins circulating in the plasma and an anionic phospholipid on the external cell membrane. However, anionic phospholipids are largely absent from the surface of most resting viable cells, suggesting that perturbation of the cell membrane is required for binding of phospholipid-binding proteins to cells. A number of cells or particles that express negatively charged phospholipids on their surface have been proposed as natural immunogens and/or targets for aPL. These include apoptotic cells, activated platelets, activated or injured endothelial cells, sickled red blood cells, and oxidized low-density lipoprotein (Ox-LDL) particles. In each of
the cellular examples, there is an induced loss of normal membrane phospholipid asymmetry with resultant exposure of anionic phospholipids on the cell surface.

Once an autoimmune response to a phospholipid/phospholipid-binding protein complex has been initiated, the immune response can spread to other antigens that lie within or are physically linked to the complex (i.e. ‘epitope spread’). For example, immunization with $\beta_2$GPI results in epitope spread to multiple apoptotic cell-associated antigens, presumably via the specific interaction of $\beta_2$GPI with apoptotic cells.\textsuperscript{3} Strong support for the role of epitope spread, as well as the primacy of the aPL response in human SLE, comes from recent clinical and experimental data showing that SLE autoantibodies emerge in a remarkably consistent order and can precede the development of clinical disease by 7 or 8 years.\textsuperscript{4,5} Of note, aPL are among the very first autoantibodies to appear in patients destined to develop SLE.\textsuperscript{4,5}

**Diagnosis**

A recent consensus statement has modified the criteria for classification of APS, proposing a number of important changes from previous criteria.\textsuperscript{6} A patient with APS must manifest at least one of two clinical criteria (vascular thrombosis or pregnancy morbidity) and at least one of three laboratory criteria (LAC, aCL, and/or anti-$\beta_2$GPI). Laboratory criteria must be met on two or more occasions, at least 12 weeks apart. Although prolongation of a single phospholipid-dependent coagulation assay is sufficient to establish the presence of LAC, current criteria recommend using at least two coagulation assays before excluding LAC. The two assays should evaluate distinct portions of the coagulation cascade (extrinsic, intrinsic, or final common pathways).

Recently published guidelines recommend the combination of a sensitive activated partial thromboplastin time (APTT) and the dilute Russell’s viper venom time (dRVVT).\textsuperscript{7} As opposed to the earlier classification, clinical and laboratory criteria cannot be arbitrarily separated in time, but should be greater than 12 weeks and less than 5 years apart. This requisite timing decreases the likelihood of an incidental association between laboratory and clinical events, and integrates the requirement for testing aPL on at least two occasions at least 12 weeks apart. Although the laboratory criteria have been broadened to include anti-$\beta_2$GPI antibodies (titre >99th percentile), the threshold for aCL positivity has been tightened considerably (titre >99th percentile, or >40 GPL or MPL units). Only IgM and IgG aCL and anti-$\beta_2$GPI fulfil the laboratory criteria; IgA aCL and anti-$\beta_2$GPI are still thought to lack sufficient specificity.

It is important to emphasize that these criteria are intended primarily for classification of patients entered into clinical studies on APS and are not intended as diagnostic criteria for APS in the general medical community. To minimize the incorrect attribution of APS to unaffected patients (false positives), these criteria are designed to have very high specificity. Given the inexorable trade-off between sensitivity and specificity, the sensitivity of these criteria is somewhat limited. Hence, in the clinical setting, failure to fulfil these classification criteria should not necessarily preclude the diagnosis of APS.

None of the other protean clinical manifestations of APS, such as thrombocytopenia or livedo reticularis, is included in the clinical criteria. Although such features
have been associated with aPL, they occur in a variety of disease states other than APS and their specificity for APS does not reach that of vascular thrombosis. The consensus statement has also proposed standardized definitions for multiple clinical features of APS, such as aPL-associated nephropathy, which are not included in the classification criteria but are relevant to the syndrome.\textsuperscript{6}

### Classification of APS

Earlier classifications divided APS into several categories. ‘Primary’ APS referred to APS in patients without clinical evidence of another autoimmune disease, whereas ‘secondary’ APS referred to APS in association with autoimmune or other diseases, of which SLE is by far the most frequent. The recent consensus statement has recommended abandoning this distinction. Although most patients with so-called secondary APS have SLE, some patients with APS have clinical and/or laboratory evidence of autoimmune disease and yet do not fulfil the American College of Rheumatology criteria for SLE. Moreover, the clinical manifestations of APS do not appear to differ between patients with and without SLE. For these reasons, the current classification criteria for APS recommend documentation of the co-existence of APS with SLE or other diseases, rather than distinguishing specific categories of APS.\textsuperscript{6}

The link between aPL and rheumatological diseases other than SLE (with the exception of rheumatoid arthritis, and possibly Sjögren’s syndrome and systemic sclerosis) is more tenuous and based largely on case reports.\textsuperscript{1,8} Many cases of Sneddon’s syndrome, defined as the clinical triad of stroke, livedo reticularis, and hypertension, may represent undiagnosed APS. In contrast, aPL occurring in association with other conditions (including drugs, infections, malignancy, and haemodialysis) are usually low-titre IgM antibodies and not associated with thrombotic events. ‘Catastrophic’ APS will be discussed separately below.

### Epidemiology

aPL are found relatively infrequently among healthy controls, with a prevalence of 1–5\% for each of aCL, anti-\(\beta_2\)GPI, and LAC. As with other autoantibodies, the frequency of aPL increases with age, especially among elderly patients with co-existent chronic diseases. Among patients with SLE, the frequency of aPL is much higher, ranging from 12\% to 30\% for both aCL and anti-\(\beta_2\)GPI and 15\% to 34\% for LAC. These percentages predate the most recent consensus statement, and application of its revised stricter laboratory criteria may lead to a significant lowering of these estimates of aPL prevalence.

Many patients have laboratory evidence of aPL without clinical consequence. For otherwise healthy controls, there are insufficient data to determine what percentage of aPL-positive individuals will eventually have a thrombotic event or pregnancy complication consistent with APS. The multi-factorial nature of thrombosis makes it difficult to assess the annual risk of thrombosis in patients with aPL. In a recent trial of primary prophylaxis among unselected patients with aPL, of whom ~85\% had a systemic rheumatological disease, the annual risk of thrombosis was between 0 and 2.8\%.\textsuperscript{9} The percentage
of aPL-positive SLE patients who have or develop APS is as high as 50–70% after 20 years of follow-up. On the other hand, up to 30% of aCL-positive SLE patients lacked any clinical evidence of APS over an average follow-up of 7 years.

**Which patients with aPL will develop thrombosis?**

Identification of those patients with aPL who are at increased risk for a thrombotic event is a critical issue that continues to elude us. In general, LAC are considered the most specific predictors of APS, whereas aCL are the least specific, and anti-β2GPI are of intermediate specificity. In a meta-analysis of 25 studies involving over 7000 patients, the mean risk for thrombosis was increased 11.0-fold by LAC versus 1.6-fold by aCL. The specificities of aCL and anti-β2GPI for APS increase with titre, and are higher for IgG versus IgM isotype. Still, there is no definitive association of specific clinical manifestations with particular aPL subsets. Therefore, multiple aPL tests should be used, as patients may be positive in one test and negative in another.

The most important risk factor for thrombosis in APS, and the only one sufficiently predictive to warrant treatment, is a previous history of thrombosis. Other risk factors, each of which may increase the risk for thrombosis up to 10-fold, include: the presence of LAC, an elevated titre of IgG aCL or IgG anti-β2GPI, persistence of aPL, and the co-existence of all three aPL (LAC, aCL, and anti-β2GPI). The concomitant presence of multiple aPL seems a particularly potent marker of thrombosis (odds ratio [OR] as high as 33), with the cumulative incidence of thrombosis approaching 50% after 10 years and almost 30% of warfarin-treated patients still experiencing a thrombotic event.

There are additional specific features of aPL that may help to stratify risk, but they are not yet integrated into clinical practice. For example, β2GPI-dependent LAC demonstrate a much stronger association with thrombosis (OR ~42) than LAC that are independent of β2GPI (OR ~1.6). Moreover, among anti-β2GPI, those that recognized Domain I of β2GPI were predictive of thrombosis (OR ~19), whereas antibodies that recognized β2GPI domains other than Domain I showed no association with thrombosis. Interestingly, the reactive epitope on Domain I is inaccessible to antibody when β2GPI is in solution, but is exposed when β2GPI binds to anionic phospholipid and undergoes a conformational change.

Elevated levels of D-dimer (a product of fibrinolysis, and therefore an indicator of clot formation) have been shown to be a harbinger of future thrombosis among non-APS patients following completion of a standard course of anticoagulation (≥3 months) for an unprovoked venous thrombo-embolism (OR=2.2). Preliminary data suggest that D-dimer levels may also be used to predict thrombotic risk among aPL-positive SLE patients. D-dimer levels correlated with both thrombosis and the presence of aPL. Although D-dimer levels were usually elevated for months before a thrombotic event, SLE flares and systemic infection also seemed to increase production of D-dimer.

**Pathogenesis of APS**

The cellular and molecular mechanisms by which aPL promote thrombosis remain largely unclear. Currently, there are three major theories as to how aPL may mediate a
The procoagulant effect in vivo. The first theory proposes that aPL interfere with the normally protective function of β2GPI, which is to coat the surface of negatively charged cells or particles (e.g., apoptotic cells or Ox-LDL, respectively) and allow them to remain in the circulation without causing procoagulant activity. By binding to β2GPI-coated cells/particles and creating immune complexes with β2GPI, aPL promotes the phagocytic uptake of these cells/particles, thereby inducing a proinflammatory response. This mechanism may have especial relevance with respect to Ox-LDL, a major contributor to atherosclerosis that is present at sites of oxidative injury to vascular endothelium. The second theory proposes that aPL stabilize the otherwise weak interaction of phospholipid-binding proteins such as β2GPI to the surface of healthy cells (e.g., endothelial cells) and, in this way, interfere with the binding of other essential phospholipid-binding proteins, such as the anticoagulant protein annexin A5. The third theory proposes that aPL-mediated dimerization of β2GPI on a cell surface (e.g., endothelial cells, platelets, or monocytes) results in activation of the cell. Current thinking, however, is that in and of itself, dimerization of β2GPI is insufficient to activate cells, and that additional factors, involving innate immune activation, are required to create a proinflammatory microenvironment in which thrombosis can occur.

**Differential diagnosis**

APS is one of several prothrombotic states in which thrombosis can occur in either the arterial or the venous bed (cf. table 4 in ). Although other conditions predisposing to arterial and venous thrombosis may be detected through routine laboratory testing, the existence of aPL may be the sole abnormality in a patient with primary APS. As a normal APTT does not exclude the presence of LAC, a patient presenting with a first thrombotic event should be screened for LAC by at least two LAC-sensitive assays, as well as for aCL and anti-β2GPI. Importantly, diagnosis may be unsuspected in cases where APS results in a chronic, more indolent process, leading to ischaemia and slowly progressive loss of renal or other organ function.

It is also important to monitor secondary risk factors that increase the tendency to thrombosis. Such factors can affect the arterial or venous beds, and include stasis, vascular injury, medications such as oral contraceptives, and established risk factors for atherosclerotic disease (e.g., diabetes, hypertension, smoking, and serum lipid abnormalities). Assessment for microalbuminuria (a putative marker of innate immune activation) and for chronic kidney disease (CKD) should also be performed. Recent data suggest that the risk factors for arterial versus venous thrombosis may differ, and that patients developing these events may represent distinct populations. Effective prophylaxis of arterial versus venous thromboses, apart from anticoagulation, may therefore entail different strategies.

As the presence of aPL alone may be insufficient to generate thrombosis, the elimination or reduction of risk factors is especially important. These risk factors may constitute a ‘second hit’, likely to lead to some form of endothelial cell activation or injury. Such a ‘second hit’, in combination with aPL, may be required for thrombosis to occur. However, even in patients with documented APS, it is often difficult to disentangle the risk factor from the outcome. For example, APS is associated with the
nephrotic syndrome, itself a risk factor for thrombo-embolism. Similarly, thrombotic microangiopathy (TMA) of the kidney can lead to severe hypertension, which may be mistaken as the cause, rather than the result, of the TMA.

**General clinical features**

Although clinical manifestations are most clearly attributed to aPL in primary APS, the clinical consequences of aPL are similar in all patients with APS, regardless of disease association. Any organ can be involved, and the range of disorders observed within any organ system spans a diverse spectrum (cf. table 5 in 1). The effects of aPL are best appreciated from a pathogenetic point of view, with emphasis placed on two key features: (1) nature and size of the vessels involved; and (2) acuteness or chronicity of the thrombotic process.

Venous thrombosis, in particular deep venous thrombosis of the lower extremities, is the most common manifestation of APS. Up to 50% of these patients suffer pulmonary emboli. Arterial thromboses are less common than venous thromboses in APS, and most events show features consistent with ischaemia or infarction. The severity of presentation relates to the acuteness and extent of occlusion. It should be emphasized that thrombotic episodes frequently occur in vascular beds atypically affected by other prothrombotic states, such as the subclavian, renal, retinal, and pedal arteries. Moreover, not all arterial episodes of ischaemia and/or infarction are thrombotic in origin. Emboli, especially from mitral or aortic valve vegetations, can also lead to vascular occlusion and organ ischaemia, especially in the cerebrovascular circulation.

Acute involvement at the level of the capillaries, arterioles, or venules often results in a clinical picture virtually indistinguishable from that of haemolytic uraemic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP) and other causes of TMA. The existence of TMA often goes unrecognized, because its clinical manifestations mimic those of more common diseases and conditions, such as sepsis, that occur in acutely ill patients. For example, TMA of the pulmonary microvasculature can manifest as capillary leak syndrome or alveolar haemorrhage, whereas TMA of the brain and heart can produce clinical pictures resembling diffuse cerebritis and myocarditis, respectively.

Importantly, TMA may also occur as a more chronic process, resulting in slow progressive loss of organ function, the underlying reason for which may only be determined by biopsy. Thus, organ involvement in APS can present anywhere along a spectrum from explosive and rapidly progressive disease to clinically silent and indolent damage. Depending on the size of vessels affected, organ failure has two predominant aetiologies, TMA or ischaemia secondary to thrombo-embolic events.

Although the most characteristic clinical features of APS relate to thrombo-embolic phenomena, other prominent manifestations of APS include thrombocytopenia, heart valve lesions, and livedo reticularis.

**Renal manifestations**

APS is associated with a broad spectrum of renal diseases (Tables 8.1 and 8.2). Renal lesions attributable to aPL do not appear to differ in APS patients with and
without SLE. As with systemic findings in APS, the renal manifestations are best understood from a pathophysiological perspective with emphasis on two features: 1) nature and size of the involved vessels; and 2) acuteness versus chronicity of the thrombotic process.

### Renal artery lesions

Renal artery involvement in APS can be bilateral and generally consists of occlusive lesions resulting from in situ thrombosis or from embolism from either a pre-existing upstream arterial lesion or a bland cardiac valvular lesion. These lesions can manifest in multiple ways, ranging from renal infarction to ischaemic acute kidney injury (AKI) to slowly progressive ischaemic CKD to renovascular hypertension. Clinical features for these syndromes in aPL-positive patients are similar to those in patients lacking aPL. In the absence of concomitant cardiac disease, hypertension is almost always present.

### Table 8.1 Renal lesions and syndromes associated with anti-phospholipid syndrome*

<table>
<thead>
<tr>
<th>Renal arterial lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>◆ Renal artery stenosis</td>
</tr>
<tr>
<td>◆ Renal artery occlusion</td>
</tr>
<tr>
<td>◆ Renal infarction</td>
</tr>
<tr>
<td>◆ Renal ischaemia</td>
</tr>
<tr>
<td>◆ Renovascular hypertension</td>
</tr>
<tr>
<td>◆ Ischaemic acute kidney injury</td>
</tr>
<tr>
<td>◆ Chronic kidney disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal vein lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>◆ Renal vein thrombosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thrombotic microangiopathy (TMA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>◆ Acute kidney injury</td>
</tr>
<tr>
<td>◆ Chronic kidney disease</td>
</tr>
<tr>
<td>◆ Subnephrotic range proteinuria</td>
</tr>
<tr>
<td>◆ Nephrotic syndrome</td>
</tr>
<tr>
<td>◆ Haematuria</td>
</tr>
<tr>
<td>◆ Malignant hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glomerular lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>◆ Membranous glomerulonephritis</td>
</tr>
<tr>
<td>◆ Focal ischaemic changes consistent with chronic TMA</td>
</tr>
<tr>
<td>◆ Other (minimal change disease, focal segmental glomerulosclerosis, mesangial C3 deposition)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adrenal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Adapted from [2].</em></td>
</tr>
</tbody>
</table>

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Table 8.2  Renal histopathological manifestations of anti-phospholipid syndrome* †

<table>
<thead>
<tr>
<th>Pathophysiological process</th>
<th>Glomeruli</th>
<th>Vasculature</th>
<th>Tubules and interstitium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute TMA</td>
<td><strong>Light</strong>: Intracapillary fibrin thrombi</td>
<td><strong>Light</strong>: Fibrin and/or fibrocellular thrombi (arteries and arterioles)</td>
<td><strong>Light</strong>: Mild oedema</td>
</tr>
<tr>
<td></td>
<td>Glomerular congestion</td>
<td>Degeneration and loss of endothelial lining</td>
<td>Mild cellular infiltrate (plasma cells and lymphocytes)</td>
</tr>
<tr>
<td></td>
<td>Endothelial cell swelling and degeneration</td>
<td>Medial accumulation of fibrinous or cellular material</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td></td>
<td>Focal mesangiolysis and mesangial hypercellularity</td>
<td><strong>Fibrinoid necrosis</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>IF</strong>: Glomerular capillary wall staining for fibrin-related antigens</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Virtual absence of staining for complement or immunoglobulins</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>EM</strong>: Separation of endothelium from glomerular basement membrane by fluffy electrolucent material</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absence of electron-dense deposits</td>
<td></td>
</tr>
<tr>
<td>Chronic TMA</td>
<td><strong>Light</strong>: Global glomerulosclerosis</td>
<td><strong>Light</strong>: Thrombotic organization with recanalization</td>
<td><strong>Light</strong>: Interstitial fibrosis</td>
</tr>
<tr>
<td></td>
<td>Occasional focal segmental glomerulosclerosis</td>
<td>Fibrous intimal hyperplasia</td>
<td>Tubular atrophy</td>
</tr>
<tr>
<td></td>
<td>Glomerular hypoperfusion</td>
<td>Intimal accumulation of connective tissue components (collagen and elastin)</td>
<td>Focal cortical atrophy</td>
</tr>
<tr>
<td></td>
<td>Double contour or ‘tram-tracking’ of capillary walls</td>
<td>Arterio- and arteriolosclerosis</td>
<td>Tubular thyroidization</td>
</tr>
<tr>
<td></td>
<td>Mesangial sclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>IF</strong>: Trace staining for fibrin-related antigens</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>EM</strong>: Glomerular basement membrane widening with mesangial interposition</td>
<td></td>
</tr>
</tbody>
</table>
The prevalence of renal artery lesions is difficult to estimate, as many lesions are clinically silent and incidentally detected by radiographic procedures or autopsy. However, among unselected patients with APS, the estimated prevalence of renal infarction is $\sim 1\%$. The prevalence of renal artery stenosis is probably greater, up to $7\%$ in unselected patients with APS and perhaps $\geq 10\%$ in APS patients selected for evidence of renal involvement of any sort (e.g., hypertension or proteinuria). Although extremely rare, abrupt complete occlusion of the renal artery can also occur.\(^{23}\)

Renal vein lesions

Renal vein thrombosis occurs more commonly in APS patients with SLE ($\sim 10\%$) than in patients without SLE ($\leq 1\%$). This is likely to be due to the multiple additional aetiologies for heavy proteinuria and nephrotic syndrome in SLE patients. Like renal artery lesions, renal vein thrombosis can be bilateral. Clinical features resemble those of renal vein thrombosis of any cause, and can include loin pain, haematuria, enlarged kidneys, and pulmonary embolism.

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**Table 8.2** (continued) Renal histopathological manifestations of anti-phospholipid syndrome*.$^1$

<table>
<thead>
<tr>
<th>Pathophysiological process</th>
<th>Glomeruli</th>
<th>Vasculature</th>
<th>Tubules and interstitium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischaemia due to large vessel thrombosis</strong></td>
<td>Light: Global glomerulosclerosis (late) Retraction or shrinkage of glomerular tuft Capillary collapse Wrinkling of capillary walls Hyperplasia of juxtaglomerular apparatus Cystic enlargement of Bowman’s space</td>
<td>Light: Arterio- and arteriolosclerosis</td>
<td>Light: Interstitial fibrosis Tubular atrophy Focal cortical atrophy Tubular thyroidization</td>
</tr>
</tbody>
</table>

* Adapted from\(^2\).

† The recent international consensus statement\(^6\) has provided a definition of aPL-associated nephropathy (APLN). APLN is the co-existence of anti-phospholipid (aPL) antibodies plus 1) histological evidence of TMA involving both arterioles and glomerular capillaries, and/or 2) one or more of the following: (a) fibrous intimal hyperplasia involving organized thrombi (with or without recanalization); (b) fibrous and/or fibrocellular occlusions of arteries and arterioles; (c) focal cortical atrophy; and (d) tubular thyroidization (large areas of tubular atrophy containing eosinophilic casts). Vasculitis, haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura, malignant hypertension or other reasons for these lesions must be excluded. If systemic lupus erythematosus is present, lesions associated with APLN must be carefully distinguished from those of lupus nephropathy.

EM, electron microscopy; IF, immunofluorescence; TMA, thrombotic microangiopathy.
TMA
The most important renal manifestation of APS is likely to be TMA, which can vary widely in presentation from an explosive AKI, requiring dialysis, to a mild progressive CKD with bland urine. TMA may be present in ≥50% of primary APS patients who have renal findings of any sort, including hypertension and minimal levels of proteinuria. Among SLE patients with APS and renal findings, the frequency of TMA is somewhat lower (albeit still ≥10%), as these patients have additional non-APS-related reasons for renal abnormalities.

Pathological changes associated with TMA are non-specific and can occur as part of several well-defined clinical entities or syndromes. For this reason, depending on the dominant mode of clinical presentation, TMA in association with APS has been variously described in the literature as any of the following: HUS/TTP; malignant hypertension; ‘renal crisis’ of scleroderma; or pregnancy-related events such as eclampsia, pregnancy-associated renal failure, post-partum renal failure, or HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets). It is critical to recognize that, irrespective of the name of the syndrome associated with TMA, the pattern of injury seen on renal biopsy is remarkably similar. Renal pathological and/or clinical differences relate far less to the associated syndrome or state (e.g., pregnancy versus non-pregnancy) than to the acuteness or chronicity of the underlying thrombotic process. Acute TMA presents suddenly, often with widespread intrarenal thrombosis and rapidly progressive AKI, whereas chronic TMA is a more smouldering process, characterized by extensive healing and scarring. Unfortunately, chronic TMA may be overlooked clinically and morphologically because of the focal, non-specific, and often subtle nature of the vascular lesions.

Although the clinical presentation of TMA is extraordinarily varied, the following generalizations may be helpful. First, hypertension, frequently severe or malignant, is extremely common (≥80%). Second, proteinuria exceeding 100 mg/day occurs in up to 90% of patients, and may achieve the nephrotic range in as many as 20% of patients. Many of these cases of nephrotic range proteinuria had primary APS, without evidence of SLE or other rheumatological disease, so the heavy proteinuria can truly be attributed to APS. Third, renal insufficiency is frequently found at presentation, ranging from anuric AKI requiring dialysis to seemingly stable mild CKD. Although not yet validated by large cohort studies, case series suggest that APS can lead to a slow loss of renal function, without history or evidence of overt nephritis. In these cases, renal biopsy often reveals focal ischaemic changes consistent with chronic TMA.

Glomerular disease
An expanding spectrum of glomerular lesions has been described in patients with APS.\(^{24}\) In most cases of nephrotic range proteinuria associated with TMA, renal biopsy reveals a variety of non-specific changes consistent with chronic glomerular ischaemia. However, true glomerular pathology does seem to occur in patients with APS. The best documented pathology is membranous glomerulonephritis. Among 29 primary
APS patients with a variety of renal abnormalities who underwent biopsy, three had membranous glomerulonephritis. Other glomerular lesions that have been reported include minimal change, focal segmental glomerulosclerosis, and mesangial deposition of C3.

**Other**

Adrenal failure, especially in association with catastrophic APS, may lead to profound disturbances of fluids and electrolytes.

**Pathology**

The histopathological features of APS reflect a combination of several major pathophysiological processes: 1) TMA (acute or chronic); 2) ischaemia secondary to upstream arterial thromboses or emboli; and 3) peripheral embolization from venous, arterial, or intracardiac sources (Table 8.2). None of these processes has unique manifestations when occurring in association with APS. Thus, the histopathology of TMA or of arterial and venous thromboses in association with APS does not differ from that seen in other prothrombotic states. Similarly, regions of ischaemia and infarction downstream of thrombotic or embolic occlusions lack unique features.

**Acute TMA**

TMA is a consequence of microvascular involvement. Its histological features are not specific to APS and can be seen in a variety of other diseases and syndromes (e.g., HUS/TTP, malignant hypertension, scleroderma, radiation-induced injury, pregnancy-associated renal failure, and various drug-induced thrombotic microangiopathies (cyclosporine, FK506, and chemotherapeutic agents, such as mitomycin C)). Although the acute changes of TMA are usually fairly prominent, the chronic changes can be quite subtle and easily overlooked. Acute changes include capillary congestion and intracapillary fibrin thrombi, generally without inflammation. Immunofluorescence reveals a predominance of fibrin-related antigens. Histological staining for CD61, a platelet glycoprotein, may increase the sensitivity for detecting intravascular platelet aggregates, a marker of acute TMA. Immune complexes are not seen. On electron microscopy, the endothelium is separated from the glomerular basement membrane by an accumulation of fluffy electron lucent material.

**Chronic TMA**

The chronic changes of APS range from ischaemic hypoperfusion to atrophy and fibrosis, and most often occur in the absence of detectable microthrombi. They typically reflect the healing and scarring of acute lesions. The glomerular capillary walls are often thickened, with a double contour or ‘tram-track’ appearance. The mesangium may have areas of sclerosis. Fibrin staining, if present, is much less intense than that seen in acute TMA. Electron microscopy shows widening of the glomerular basement membrane, with areas of mesangial interposition and cellular debris accounting for the double contours on light microscopy. Effacement of the visceral epithelial cells from the glomerular basement membrane may also be seen, especially in patients with
significant proteinuria. Significantly less electron-lucent material is seen, and there are again no electron-dense deposits.

**Interstitial changes**

Interstitial changes, although common, are non-specific. Regions of focal cortical atrophy occur within the superficial cortex, just beneath the renal capsule, and, in the appropriate context, can be very suggestive of APS. They appear as well-demarcated foci or triangles of scarring and atrophy. Their sharp borders suggest previous infarction. Features associated with focal cortical atrophy include dense interstitial fibrosis, tubular atrophy and thyroidization (large areas of tubular atrophy with eosinophilic casts), global sclerosis of glomeruli with occasional cystic dilatation of Bowman’s capsule, and fibrous intimal hyperplasia of arteries and arterioles with positive intimal staining for fibrin.

**Vascular changes**

In APS, vascular involvement extends from the non-muscular precapillary arterioles to small muscular arteries. During the acute phase, fibrin thrombi containing fragmented blood cells narrow or occlude the vascular lumen. The thrombi eventually organize into fibrocellular and fibrous vascular occlusions, which can be recanalized by endothelialized channels. An onion-skin arrangement of intimal fibrosis is a frequent end result. The lesions of fibrous intimal hyperplasia, suggestive of APS, are usually much more cellular than those of arterio- and arteriolosclerosis.

**Interaction with lupus nephritis**

The pathological features of APS can be seen in ~33% of renal biopsies performed in SLE patients. These changes, especially the more chronic ones, occur independently of concomitant lupus nephritis, as evidenced by a lack of statistical association between the presence of APS-associated nephropathy and the World Health Organization (WHO) class of lupus glomerulopathy. If APS-associated nephropathy is restricted to glomerular microthrombosis and acute TMA, then APS-associated nephropathy correlates with more severe classes of lupus glomerulopathy. However, this may reflect the greater SLE disease activity index (SLEDAI) of patients with APS-associated nephropathy, leading to more severe acute changes in the kidney, arising from both aPL-dependent and aPL-independent mechanisms.

**Other changes**

In primary APS, true vasculitis is rarely, if ever, seen. In APS in the presence of SLE, vasculitis is attributable to SLE, not APS. Although enormous confusion exists regarding terminology for the vascular lesions associated with SLE, vaso-occlusive disease in association with APS, irrespective of the size of the vessel involved, is universally due to thrombosis.

**Impact of aPL on lupus nephropathy**

There are two important and unresolved questions relating to the impact of aPL on the natural history of lupus nephropathy. The first is whether TMA or other APS-like
pathology can occur in SLE patients through mechanisms independent of aPL. A recent study strongly suggests that the answer to this first question is no, as APS-like pathology was found virtually always in association with positive aPL. The authors examined 151 consecutive renal biopsies for SLE. The definitions were precise and specific. aPL were positive only if detected on two occasions, at least 6 weeks apart. APS-like nephropathy was defined in accord with the updated consensus statement and required the presence of one of the following: TMA, focal cortical atrophy, fibrous intimal hyperplasia, or organized thrombi with or without recanalization. APS-like nephropathy was found in 32 of 81 aPL-positive patients, and only three of 70 aPL-negative patients. Of the three aPL-negative patients, two had single measurements of high-titre aCL.

The second question is the potential impact of aPL on the course and progression of renal disease in patients with SLE. Data from earlier studies are conflicting. In general, those studies finding a positive association between aPL and renal disease were based on meticulous analysis of biopsy findings rather than broad definitions of nephropathy. A recent prospective follow-up study of 111 SLE patients compared the course of aPL-positive (n=29) with that of aPL-negative (n=82) patients. By Kaplan–Meier analysis, the incidence of renal insufficiency (creatinine ≥1.5 mg/dl) was significantly greater in aPL-positive patients. A significant difference did not emerge until fairly late (>10 years). By multi-variate analysis, the presence of aPL was independently associated with an approximately twofold increased risk for the development of renal insufficiency. These data are supported by a retrospective study of 114 SLE patients who underwent renal biopsy. By multi-variate analysis, the presence of APS-associated nephropathy, independent of WHO class of lupus glomerulopathy, was a strong predictor of an elevated creatinine, hypertension, and interstitial fibrosis (OR 3.0, 2.6, and 5.4, respectively).

Catastrophic APS

In most patients with APS, thrombotic events occur singly. Recurrences may occur months or years after the initial event. However, a minority of APS patients present with an acute and devastating syndrome characterized by multiple simultaneous vascular occlusions throughout the body, often resulting in death. Although as many as 50% of catastrophic APS cases represent the very first aPL-related clinical event, catastrophic APS only accounts for <1% of all APS. Preliminary criteria for the classification of this syndrome, termed ‘catastrophic APS’, have recently been published and validated. Definitive diagnosis requires the simultaneous APS-related involvement of at least three different organ systems in a period of less than a week with histopathological confirmation of small vessel occlusion in at least one organ system. The high mortality of catastrophic APS may preclude laboratory confirmation of the presence of aPL on a second occasion at least 6 weeks later. For this reason, preliminary criteria for a probable diagnosis of catastrophic APS have also been provided.

Although the same clinical manifestations seen with non-catastrophic APS also occur as part of catastrophic APS, there are important differences in prevalence and in the calibre of the vessels predominantly affected. Large vessel venous or arterial
thrombosis is less common in patients with catastrophic APS (23% and 11% of patients, respectively), who tend to present with an acute TMA affecting small vessels of multiple organs. The kidney is the organ most commonly affected by catastrophic APS (70–80%), followed by lungs, central nervous system, heart, and skin, each of which is involved in more than 50% of cases. Hypertension is found in virtually 100% of patients. Another fulminant process that can affect up to 20% of patients with catastrophic APS is disseminated intravascular coagulation, which does not occur in non-catastrophic APS. Microvascular manifestations of catastrophic APS include the following: renal TMA; adult respiratory distress syndrome; cerebral microthrombi and microinfarctions; and myocardial microthrombi. Virtually all patients with renal involvement have hypertension, often malignant, and up to 25% require dialysis. On kidney biopsy, the pathological changes reflect the acuteness of involvement, with virtually all patients having fibrin and platelet thrombi and acute TMA. Mortality is 50%, usually secondary to multi-organ failure.

Precipitating factors of catastrophic APS include infections (22%), surgical procedures (including such minor procedures as biopsies or dental extractions) (10%), withdrawal of or inadequate anticoagulation, drugs such as oral contraceptives, obstetric complications, neoplasia, and SLE flares. A precipitating event cannot be identified in ~50% of cases. Although the pathophysiology of this disorder is poorly understood, thrombosis can be self-perpetuating in patients with an underlying hypercoagulable state. Thus, an initial thrombosis in an APS patient may upset the balance of haemostasis and set in motion a process termed ‘thrombotic storm’, leading to multiple coagulative events throughout the body.

Recommendations for the treatment of catastrophic APS are based entirely on case reports and series. Initial treatment in suspected cases involves anticoagulation with intravenous heparin plus high doses of steroids. If life-threatening, plasma exchange and/or administration of intravenous immunoglobulin should be added. The rationale for plasmapheresis derives from the documented effectiveness of plasmapheresis in treating HUS/TTP. In the absence of clinical improvement, other therapies may be used, such as cyclophosphamide, prostacyclin, fibrinolytic agents like streptokinase and urokinase, or rituximab (anti-CD20 chimeric monoclonal antibody). As thrombosis tends to be a self-perpetuating process, an early aggressive therapeutic approach is warranted in these patients.

The long-term outlook for patients surviving an episode of catastrophic APS is very much a matter of perspective. Of 58 patients followed for an average of 5.5 years, none had a recurrence of catastrophic APS, and 38 (65%) were alive without further complications of APS. Mortality occurred in nine patients (16%), and an additional 11 patients (19%) had further manifestations of APS.

**Treatment**

Treatment decisions fall into four main categories: prophylaxis, prevention of further large vessel thromboses, treatment of acute TMA, and management of pregnancy in association with aPL. Here we review data on treatment in the first two areas only. Treatment of acute TMA has been covered in the section on catastrophic APS, and treatment of obstetrical complications has been covered in a previous review.
It is important to emphasize that controlled studies do not exist with reference to the effect of treatment on the renal manifestations of APS. This lack is especially significant in that APS-associated renal disease appears to reflect microvascular events (acute and chronic TMA) more than macrovascular events (large vessel arterial and venous thrombosis). As the risk factors for microvascular thrombosis are not necessarily the same as those for arterial and venous thrombosis, extrapolation of the available literature (which focuses on macrovascular extra-renal events) to APS-associated renal diseases should be undertaken with care.

**Prophylaxis**

The literature does not support the effectiveness of aspirin in primary prevention of thrombosis. A nested case–control study within the Physicians’ Health Study examined the role of aspirin (325 mg/day) as a prophylactic agent. Aspirin offered no protection against deep venous thrombosis and pulmonary embolus in male physicians with aCL. In a recent randomized, double blind, placebo controlled trial, low-dose aspirin (81 mg/day) was no different from placebo in the prevention of a first thrombosis among asymptomatic, persistently aPL-positive individuals, most of whom had SLE or another systemic rheumatological disease. Although this study has been criticized as being underpowered, because of its small sample size (∼100 patients) and low incidence of thrombosis, it is noteworthy that virtually all thrombotic events occurred in individuals with additional risk factors.

In contrast, several smaller studies suggest a benefit to aspirin. A retrospective analysis of women with APS, identified solely by pregnancy loss, showed that low-dose aspirin (81 mg/day) significantly reduced the rate of non-gravid thrombotic events. A cross-sectional study also suggested a prophylactic benefit of low-dose aspirin in aPL-positive patients without SLE. Finally, a longitudinal analysis of aPL-positive SLE patients found that a longer duration of low-dose aspirin usage protected against thrombosis. On balance, given the low risk associated with low-dose aspirin, it seems reasonable to recommend that its usage in aPL-positive individuals be in accord with traditional guidelines for the prevention of cardiovascular disease.

Hydroxychloroquine may also be protective against the development of thrombosis in aPL-positive patients, especially in the setting of SLE. Although controlled studies are lacking, in the absence of a specific contraindication to the use of hydroxychloroquine, it seems reasonable to add this agent to the regimen of aPL-positive SLE patients.

A major role in prophylaxis should be given to the elimination of any factors predisposing to thrombosis (cf. table 4 in ). Data are emerging that these risk factors may be distinct for arterial versus venous events. Finally, modification of secondary risk factors for atherosclerosis seems prudent, based on the putative role of vascular injury in promoting aPL-associated thrombosis.

**Treatment after a thrombotic event**

A beneficial role for anticoagulation in decreasing the rate of recurrent thrombosis has been definitively shown in three retrospective studies. In a small series of
19 APS patients, recurrence at 8 years was 0% for those patients receiving oral anticoagulation. Among patients whose anticoagulation was stopped, recurrence was 50% at 2 years, and 78% at 8 years. In two larger series, protection (venous and arterial) correlated directly with the level of anticoagulation. Among 70 APS patients, intermediate- (INR (International Normalized Ratio), 2.0–2.9) and high- (INR ≥3.0) intensity treatment with warfarin significantly reduced the rate of thrombotic recurrence, whereas low-intensity treatment (INR ≤1.9) conferred no protection. Similar results were found in a series of 147 APS patients. In both studies, aspirin alone was ineffective in reducing the rate of thrombotic recurrence.

A number of additional points warrant mention. First, two recent prospective randomized controlled trials have established that intermediate-intensity treatment with warfarin (INR, 2.0–3.0) is equally as effective as high-intensity treatment (INR, 3.0–4.0) for APS patients with no history of thrombosis while on anticoagulation. Some authorities now suggest that these results should be applied only to patients for whom APS was diagnosed on the basis of a venous thrombosis, as a majority of patients in both studies (70–80%) had venous events, and patients with recurrent thromboses were excluded. Moreover, in those instances where the data are available, the INR at the time of thrombotic recurrence was <3.0 in 86% cases, regardless of the treatment arm to which the patients were assigned. Based on these data, some authorities recommend that high-intensity warfarin should be used for APS patients with an arterial thrombosis and/or multiple thrombotic events. Second, discontinuation of warfarin seems to be associated with an increased risk of thrombosis, and even death, especially in the first 6 months after stopping anticoagulation. As the rate of recurrence among patients who are not optimally anticoagulated can be as high as 70%, most authorities (although not all) recommend that treatment with warfarin should be long term, if not lifelong. Finally, monitoring the level of anticoagulation in APS patents is complicated by two factors: 1) the differing contribution of vitamin K-dependent factors to prolongation of the INR (for which factor VII is most important) versus therapeutic efficacy of warfarin (for which prothrombin (factor II) may be most important); and 2) potential interference by aPL in measurement of the INR. aPL interference is most common among patients whose INR is elevated prior to initiation of treatment. In such cases, monitoring of prothrombin levels is recommended.

Additional treatments

A theoretical basis exists for suggesting that statins and angiotensin converting enzyme inhibitors (ACEI), two agents already commonly prescribed by nephrologists, may be effective in decreasing thrombotic events in patients who have aPL. Statins were effective in an in vivo animal model of APS, and appear to have beneficial anti-inflammatory and anti-thrombotic effects on the vascular endothelium. In addition, both statins and ACEI inhibit monocyte expression of tissue factor, a co-factor in the coagulation cascade that is up-regulated by interaction with aPL. Besides their established role in cardiovascular protection, statins have also been shown to prevent venous thrombosis. Given the favourable therapeutic profile of these agents, and the prevalence of renal disease among APS patients, the use of ACEI, and probably statins, seems to be justified.
Other potential therapies, poised for clinical trials, include rituximab, factor Xa inhibitors (e.g., rivaroxiban and fondaparinux), complement inhibitors, and p38 mitogen-activated protein kinase inhibitors.  

**Take home points**

1. In utilizing the consensus criteria for classification of APS, it is important to note the following key points:
   - the criteria are intended primarily for classification of patients entered into clinical studies rather than as clinical diagnostic criteria for APS;
   - the diagnosis of APS requires that a patient with APS manifest at least one of two clinical criteria (vascular thrombosis or pregnancy morbidity) and laboratory detection of aPL (i.e. LAC, aCL, and/or anti-β2GPI);
   - the criteria recommend documentation of the co-existence of SLE or other diseases, as well as the co-existence of specific risk factors for vascular thrombosis, rather than distinguishing specific categories of APS.

2. In general, LAC are considered the most specific predictor of APS, anti-β2GPI are of intermediate specificity, and aCL are the least specific. Multiple aPL tests should be used, as patients may be positive in one test and negative in another.

3. As macrovascular thrombosis in APS can occur in either the arterial or the venous bed, it is important to monitor secondary risk factors that are specific to these beds, including stasis, vascular injury, medications such as oral contraceptives, and established risk factors for atherosclerotic disease.

4. Venous thrombosis, in particular deep venous thrombosis of the lower extremities, is the most common manifestation of APS, with up to 50% of APS patients suffering pulmonary emboli.

5. Arterial thromboses are less common than venous thromboses in APS, and most events show features consistent with ischaemia or infarction.

6. Renal lesions attributable to APS do not differ significantly in patients with and without concomitant SLE, and are best understood from a pathophysiological perspective, with emphasis on two features: 1) the nature and size of the involved vessels, and 2) the acuteness versus chronicity of the thrombotic process.

7. Renal arterial involvement in APS generally consists of occlusive lesions resulting from either *in situ* thrombosis or embolism from an upstream source. These lesions are commonly asymptomatic and detected incidentally.

8. Renal vein thrombosis occurs more frequently in APS patients with SLE (∼10%) than in patients without SLE (≤1%), most likely because of SLE-associated proteinuria and nephrotic syndrome.

9. The most important renal manifestation of APS is TMA, which can vary widely in presentation, from an explosive AKI requiring dialysis to a mild progressive CKD. TMA may be present in ≥50% of primary APS patients with renal findings of any sort, including hypertension, microscopic haematuria, and/or minimal levels of proteinuria.
10. The renal histopathological features of APS reflect a combination of two major pathophysiological processes: 1) TMA (acute or chronic); and 2) ischaemia secondary to upstream arterial and/or arteriolar lesions.

11. A minority (<1%) of APS patients presents with ‘catastrophic APS’, characterized by multiple simultaneous organ involvement and failure, often resulting in death. Large vessel thrombosis is less common in patients with catastrophic APS, who tend to present with an acute TMA affecting the microvasculature of multiple organs.

12. The most important risk factor for thrombosis in APS, and the only one sufficiently predictive to warrant treatment, is a previous history of thrombosis.

13. The literature does not support the effectiveness of aspirin for primary prophylaxis of thrombosis in aPL-positive patients. On balance, however, given the minimal risk associated with low-dose aspirin, it seems reasonable to recommend its usage in aPL-positive individuals, in accord with traditional guidelines for the prevention of cardiovascular disease.

14. Although controlled studies are lacking, hydroxychloroquine may be protective as a primary prophylactic agent against the development of thrombosis in aPL-positive patients, especially in the setting of SLE.

15. A major role in prophylaxis should also be given to elimination of non-aPL-associated risk factors for thrombosis, as well as to modification of secondary risk factors for atherosclerosis.

16. A beneficial role for anticoagulation in decreasing the rate of recurrence of thrombosis has been shown. In two prospective randomized controlled trials of warfarin, intermediate-intensity treatment (INR, 2.0–3.0) was as effective as high-intensity treatment (INR, 3.0–4.0). Some authorities, however, recommend high-intensity warfarin for APS patients with an arterial thrombosis and/or multiple thrombotic events, as a majority of patients in both studies had venous events, and patients with recurrent thromboses were excluded.

17. The use of statins, and probably ACEI, seems justified for both primary and secondary prophylaxis in APS, given the favourable therapeutic profile of these agents, their potentially beneficial anti-inflammatory and anti-thrombotic effects, and the high prevalence of renal disease among APS patients.

References

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest


* Older, but still relevant, review of general features of APS.


** Excellent and still the most comprehensive clinical series revealing the renal pathological changes of primary APS.
** Clinical series demonstrating that the renal pathological changes of APS are essentially the same, whether APS is accompanied by SLE or not.
* Excellent clinical study demonstrating a tight correlation between aPL-associated nephropathy and laboratory evidence of aPL. Essentially no cases of aPL-associated nephropathy were seen in the absence of aPL.
* Excellent clinical study demonstrating a tight correlation between aPL-associated nephropathy and laboratory evidence of aPL. Essentially no cases of aPL-associated nephropathy were seen in the absence of aPL.
* Clinical study demonstrating that aPL may be a risk factor for progression of CKD.
* The most recent update from the catastrophic APS registry, containing approximately 300 patients.


** Excellent and up-to-date critical review of treatment options for APS.


** Excellent and up-to-date critical review of treatment options for APS.


* One of two randomized clinical trials comparing the efficacy of two different intensities of warfarin anticoagulation in patients with definite APS.

One of two randomized clinical trials comparing the efficacy of two different intensities of warfarin anticoagulation in patients with definite APS.


* Highly influential systematic review of all treatment trials for secondary prevention of thrombosis in APS.


* Important recent trial demonstrating that statins have a role in prevention of not only arterial, but also venous, thrombotic events.

Chapter 9

Vasculitis classification

J. Charles Jennette, Ronald J. Falk, and Adil Hussein Gasim

Introduction

The hallmark of vasculitis is inflammation of vessel walls. Thus, the diagnosis of vasculitis requires recognition of signs and symptoms of vascular inflammation. However, there are numerous complexities to the diagnosis of vasculitis. First, there are numerous variants of vasculitis defined by different causes, different pathogenic mechanisms, different distributions of vessel involvement, different types of inflammatory vascular injury and different disease associations (Tables 9.1 and 9.2, and Fig. 9.1). Second, the pathological lesions of vasculitis (Fig. 9.2) are rather non-specific and evolve over time from acute to chronic inflammatory lesions to sclerosing lesions. Third, many different organs can be affected and different patients with the same vasculitis may have very different distributions of organ involvement. Fourth, many of the signs and symptoms of vasculitis are non-specific, and mimic and can be mimicked by other types of inflammatory or ischaemic single organ or multi-system disease. Fifth, the aetiology of most forms of vasculitis is poorly understood or unknown thus requiring categorization of vasculitides on the basis of clinicopathological or syndromatic definitions. And finally, in part because of the aforementioned difficulties, there is no complete agreement about how to name, categorize or diagnose most forms of vasculitis.

The lack of a unified system for diagnostic categorization has caused many problems. Distinct types of vasculitis have been given multiple names and different names have been used for the same type of vasculitis. This chapter will emphasize the Chapel Hill Consensus Conference (CHCC) Nomenclature System (Table 9.2), which was developed through a collaboration of physicians from diverse fields, including rheumatology, immunology, nephrology, pulmonology, nephrology and pathology.1** This system does not include all forms of vasculitis. For example, Behçet disease, isolated vasculitis of the central nervous system vasculitis, hypocomplementaemic urticarial vasculitis and rheumatoid vasculitis are not included and will not be discussed in this chapter. In 2006, a consensus group reported a classification system for vasculitis that is oriented toward children.2+ In this chapter, reference will be made to the proposals of a second CHCC convened in 2011. The official CHCC 2011 recommendations were not published when this chapter was written.
The CHCC Nomenclature System divides vasculitides into three groups: 1) large vessel vasculitis, 2) medium vessel vasculitis and 3) small vessel vasculitis (Table 9.2). Although these names imply that the size of the vessels affected by inflammation is the primary criterion for categorizing vasculitides, this is not the case. Figure 9.1 shows that there is substantial overlap among categories with respect to the size and type of vessel involved. In fact, adequate diagnostic categorization requires a complex integration not only of clinical data but also historical data, demographic data, serological data and pathological data to reach the proper diagnosis. The reference to vessel size is also misleading because, from a pathological perspective, the type of vessel and the type of inflammation are more specific for the major categories of vasculitis than is

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<td><strong>Large Vessel Vasculitis</strong></td>
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<td>Takayasu Arteritis</td>
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<td>Giant Cell Arteritis</td>
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<td><strong>Medium Vessel Vasculitis</strong></td>
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<td>Polyarteritis Nodosa</td>
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<td>Kawasaki Disease</td>
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<td><strong>Small Vessel Vasculitis</strong></td>
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<td>ANCA-Associated Vasculitis</td>
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<td>Microscopic Polyangiitis</td>
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<td>Granulomatosis with Polyangiitis (Wegener’s) (GPA)</td>
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<td>Eosinophilic Granulomatosis with Polyangiitis (Churg Strauss) (EGPA)</td>
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<td><strong>Immune Complex SVV</strong></td>
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<td>Anti-GBM Disease</td>
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<td>Cryoglobulinemic Vasculitis</td>
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<td>IgA Vasculitis (Henoch-Schönlein)</td>
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<td>Hypocomplementemntic Urticarial Vasculitis (Anti-C1q Vasculitis)</td>
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<td>Cogan’s Syndrome</td>
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<td>(e.g. Cutaneous Leukocytoclastic Angiitis)</td>
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<td><strong>Vasculitis Associated with Systemic Disease</strong></td>
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<td>(e.g. Lupus Vasculitis)</td>
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<td><strong>Vasculitis Associated with Probable Etiology</strong></td>
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<td>(e.g. Hepatitis B Virus-Associated Vasculitis)</td>
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### Table 9.2 Names and definitions of vasculitis adopted by the 1994 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis with proposed modifications for the names for Wegener’s granulomatosis and Churg–Strauss Syndrome (proposed by the 2011 CHCC)

<table>
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<tr>
<th>Vasculitis Type</th>
<th>Definition</th>
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<tr>
<td><strong>Large vessel vasculitis</strong></td>
<td><strong>Giant cell arteritis</strong></td>
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<td>Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 40 and often is associated with polymyalgia rheumatica</td>
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<tr>
<td><strong>Takayasu arteritis</strong></td>
<td>Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 40</td>
</tr>
<tr>
<td><strong>Medium sized vessel vasculitis</strong></td>
<td><strong>Polyarteritis nodosa</strong></td>
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<tr>
<td></td>
<td>Necrotizing inflammation of medium sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules</td>
</tr>
<tr>
<td><strong>Kawasaki disease</strong></td>
<td>Arteritis involving large, medium sized and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children</td>
</tr>
<tr>
<td><strong>Small vessel vasculitis</strong></td>
<td><strong>Wegener’s granulomatosis (polyangiitis with granulomatosis)</strong>†</td>
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<tr>
<td></td>
<td>Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium sized vessels, e.g. capillaries, venules, arterioles and arteries. Necrotizing glomerulonephritis is common</td>
</tr>
<tr>
<td><strong>Churg–Strauss syndrome</strong></td>
<td>Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium sized vessels, and associated with asthma and blood eosinophilia</td>
</tr>
<tr>
<td><strong>Microscopic polyangiitis†</strong></td>
<td>Necrotizing vasculitis with few or no immune deposits affecting small vessels, i.e. capillaries, venules or arterioles. Necrotizing arteritis involving small and medium sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs</td>
</tr>
<tr>
<td><strong>Henoch–Schönlein purpura (IgA vasculitis)</strong></td>
<td>Vasculitis with IgA-dominant immune deposits affecting small vessels, i.e. capillaries, venules or arterioles. Typically involves skin, gut and glomeruli, and is associated with arthralgias or arthritis</td>
</tr>
<tr>
<td><strong>Cryoglobulinaemic vasculitis</strong></td>
<td>Vasculitis with cryoglobulin immune deposits affecting small vessels, i.e. capillaries, venules or arterioles, and associated with cryoglobulins in serum. Skin and glomeruli are often involved</td>
</tr>
<tr>
<td><strong>Cutaneous leucocytoclastic angiitis</strong></td>
<td>Isolated cutaneous leucocytoclastic angiitis without systemic vasculitis or glomerulonephritis</td>
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* Large artery refers to the aorta and the largest branches directed toward major body regions (e.g. to the extremities and the head and neck); medium-sized artery refers to the main visceral arteries (e.g. renal, hepatic, coronary and mesenteric arteries), and small artery refers to the distal arterial radicals that connect with arterioles. Note large and medium-sized vessel vasculitides do not involve vessels other than arteries.

† Strongly associated with anti-neutrophil cytoplasmic autoantibodies (ANCA).
Fig. 9.1 Predominant vascular involvement by large vessel vasculitides, medium sized vessel vasculitides and small vessel vasculitides as indicated by the positions and heights of the solid triangles. The algorithm suggests clinical and pathological features that discriminate between different diagnostic categories of vasculitis. ANCA, anti-neutrophil cytoplasmic autoantibodies; H-S, Henoch-Schönlein; IF, immunofluorescence microscopy; Im Cx, immune complex; MCLN, mucocutaneous lymph node syndrome; SLE, systemic lupus erythematosus; yo, years old.
vessel size alone. In essence, during the active acute phase, the large vessel vasculitides manifest as granulomatous arteritis, the medium sized vessel vasculitides as necrotizing arteritis and the small vessel vasculitides as necrotizing polyangiitis.

This chapter will briefly review the distinctive features of a number of relatively common systemic vasculitides with an emphasis on features that allow diagnostic differentiation. Most of these vasculitides and their clinical management are discussed in more detail elsewhere in this book.

**Large vessel vasculitides**

The large vessel vasculitides affect the aorta and its major branches, such as those to the head and neck, and to the extremities. Takayasu arteritis and giant cell arteritis are the two major categories of large vessel vasculitis. In both, the acute phase of injury is characterized by transmural infiltration by mononuclear leucocytes (lymphocytes, monocytes and macrophages) (Fig 9.2a) with varying amounts of granulomatous

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**Fig. 9.2** Renal vasculitis: a) Takayasu arteritis affecting the main renal artery resulting in thickening of the intima (I), and transmural mononuclear leucocyte infiltration affecting the intima (I), media (M) and adventitia (far right). Within the circle is a cluster of macrophages including multi-nucleated giant cells (H&E stain). b) Kawasaki disease arteritis affecting an interlobar artery of the kidney with transmural necrotizing inflammation (e.g. circle) (I, intima; M, muscularis; A, adventitia) (H&E stain). c) ANCA disease causing necrotizing arteritis in an interlobular artery with fibrinoid necrosis (circle) (Masson trichrome stain). d) ANCA disease causing necrotizing glomerulonephritis with fibrin (F) and early crescent formation in Bowman’s space, and focal disruption of Bowman’s capsule (between arrows) (Jones silver stain).
inflammation including multi-nucleated giant cells. Chronic disease has predominantly sclerosis with scant inflammation. This less specific pathological appearance may complicate pathological diagnosis, for example leading to confusion with hypertensive arteriosclerosis or atherosclerosis. The inflammation or scarring or both cause narrowing of arteries and causes ischaemic symptoms, for example pulselessness and claudication.

Takayasu arteritis

William Savory in 1856 probably made the first detailed clinical description of Takayasu arteritis; however, patients with pulseless disease who probably had Takayasu arteritis were described as early as the mid-eighteenth century. Mikito Takayasu, for whom the disease is named, was a Japanese ophthalmologist who identified the ocular complications of this disease in 1908.

Takayasu arteritis is characterized pathologically by granulomatous inflammation that most often affects the aorta and its major branches, including the renal arteries (Fig 9.2a), but also can affect the pulmonary arteries. Synonyms include ‘aortic arch syndrome’ and ‘pulseless disease’ because the arteries arising from the aorta often are narrowed causing diminished or absent pulses, especially in the upper extremities. Frequent signs and symptoms of Takayasu arteritis include fever, arthralgias, weight loss, reduced pulses, vascular bruits, claudication and renovascular hypertension. Takayasu arteritis has been reported most often in Asia, has a strong female predilection, usually is diagnosed in individuals who are between 10 and 20 years old, and only rarely occurs after 50 years old. Patient age is very useful for distinguishing between Takayasu arteritis and giant cell arteritis because giant cell arteritis rarely occurs before 50 years old.

Giant cell arteritis

Hutchinson gave a detailed account of giant cell arteritis in 1890, in which he emphasized the involvement of the temporal arteries. This resulted in the widespread use of the term ‘temporal arteritis’ for this category of vasculitis. However, the systemic distribution of this disease is now well recognized. Thus, the term giant cell arteritis is more appropriate than temporal arteritis. In addition, not all patients with giant cell arteritis have temporal artery involvement and vasculitides other than giant cell arteritis (e.g. polyarteritis nodosa, granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA)) can cause temporal artery inflammation. Polymyalgia rheumatica is associated with giant cell arteritis, and thus is a useful aid for diagnosis. Once again, however, not all patients with giant cell arteritis have polymyalgia rheumatica, and not all patients with polymyalgia rheumatica have giant cell arteritis.

Giant cell arteritis affects the aorta and its major branches, and has a predilection for the extracranial branches of the carotid artery. Giant cell arteritis usually affects multiple body regions, but may be isolated to a single organ, such as uterus, ovary, breast and brain. Giant cell arteritis is most common in people of northern European ancestry and over 95% of patients are older than 50 years old. The most common symptom is headache.
Other common manifestations are blindness, deafness, jaw claudication, tongue dysfunction, extremity claudication and reduced pulses. Over 50% of patients with giant cell arteritis have polymyalgia rheumatica, which is characterized by stiffness and aching in the neck and the proximal muscles of the shoulders and hips. Older age, polymyalgia rheumatica and preferential involvement of branches of the carotid artery are useful in differentiating giant cell arteritis from Takayasu arteritis.

Medium vessel vasculitis

Necrotizing arteritis was first recognized because of the nodular and aneurysmal lesions in arteries that are caused by the necrotizing acute inflammation. Adolf Kussmaul and Rudolf Maier reported the first definitive description of a patient with necrotizing arteritis in 1866. Their patient had typical features of systemic vasculitis, including fever, anorexia, muscle weakness, myalgias, paresthesias, abdominal pain and oliguria. Post-mortem examination demonstrated nodular inflammatory lesions in medium sized and small arteries throughout the body. Kussmaul and Maier named the disease ‘periarteritis nodosa’, which evolved into the more appropriate term ‘polyarteritis nodosa’ referring to the involvement of multiple different arteries by transmural (not only perivascular) inflammation. Polyarteritis nodosa is now the most widely used term, and is advocated by the CHCC Nomenclature System. 

Until additional distinctive categories vasculitis with necrotizing arteritis were recognized, all patients with necrotizing arteritis were diagnosed as having polyarteritis nodosa. Over the years, however, numerous observations have confirmed that necrotizing arteritis identical to that seen in polyarteritis nodosa can occur as a component of many other clinically and pathologically distinct forms of vasculitis. For example, necrotizing arteritis that can be confused with polyarteritis nodosa also occurs in Kawasaki disease, MPA, GPA and EGPA. These different variants of vasculitis each have distinctive manifestations, natural histories and treatment requirements. Thus, it is very important to properly categorize a patient who has necrotizing arteritis rather than making a reflex diagnosis of polyarteritis nodosa.

Polyarteritis nodosa

Because of the historical use of the category polyarteritis nodosa as a wastebasket for all forms of vasculitis with necrotizing arteritis, most of the literature on polyarteritis nodosa prior to the 1990s includes conclusion based on populations of patients with various combinations of both polyarteritis nodosa and microscopic polyangiitis. Using the CHCC Nomenclature System definitions (Table 9.2), polyarteritis nodosa can be separated from microscopic polyangiitis by the absence of signs and symptoms of involvement of vessels other than arteries in polyarteritis nodosa (e.g. absence of glomerulonephritis, alveolar capillaritis, dermal venulitis) and the presence of such involvement in microscopic polyangiitis. 

Pathologically, polyarteritis nodosa is characterized in the acute phase by necrotizing arteritis, often with arterial aneurysms, which actually are pseudoaneurysms formed by erosion of the necrotizing process through the arterial walls and into adjacent tissues. Thrombosis, infarction and haemorrhage often accompany the arterial inflammation
and necrosis. Any calibre artery can be affected by polyarteritis nodosa, from the main visceral artery to the smallest of arteries, such as epineural arteries. Histologically, the lesions begin with acute inflammation and fibrinoid necrosis (Fig. 9.2c), evolve through chronic inflammation and culminate in arterial sclerosis.

Polyarteritis nodosa often involves the gastrointestinal tract, heart, kidneys, skin and peripheral nerves. The major clinical manifestations include fever, peripheral neuropathy, myalgias, abdominal pain, and signs and symptoms of renal disease. 

When reading the literature about polyarteritis nodosa, especially prior to 1990, one must determine whether data are derived from patients with polyarteritis nodosa alone (as defined in this chapter), or from patients with a mixture of polyarteritis nodosa and microscopic polyangiitis. A major distinction between polyarteritis nodosa and microscopic polyangiitis is the high frequency of glomerulonephritis and pulmonary involvement in microscopic polyangiitis but not polyarteritis nodosa. Anti-neutrophil cytoplasmic autoantibodies (ANCA) are frequent in patients with microscopic polyangiitis, as will be discussed in more detail later, however, ANCA are not frequent in patients who have arteritis that is not accompanied by inflammatory involvement of capillaries or venules. ANCA are not frequent in polyarteritis nodosa.

**Kawasaki disease**

Kawasaki disease is an acute febrile illness that usually occurs in young children. The *sine qua non* of Kawasaki disease is the mucocutaneous lymph node syndrome, which is characterized by polymorphous erythematous rash, erythema of the palms and soles, erythema of the oropharyngeal mucosa, conjunctivitis, indurative oedema and desquamation of the extremities, and non-suppurative lymphadenopathy. The mucocutaneous lymph node syndrome was first described by Tomisaku Kawasaki in 1967. Necrotizing arteritis involving medium sized and small arteries is an important complication of Kawasaki disease that was first reported by Tanaka, Naoe and Kawasaki. Kawasaki disease usually is treated with aspirin and intravenous gamma globulin therapy rather than high-dose corticosteroids and cyclophosphamide as would be used for polyarteritis nodosa.

The acute arteritis of Kawasaki disease is a necrotizing process that usually has less conspicuous fibrinoid necrosis than polyarteritis nodosa (Fig. 9.2c). Early inflammatory changes are most extensive in the media and are characterized by oedema and disassociation of smooth muscle cells. Transmural involvement eventually occurs, and there may be extensive intimal thickening or thrombosis, or both, that can cause ischaemia and infarction.

The arteritis of Kawasaki disease affects small and medium sized arteries, and frequently involves the coronary arteries. This may result in coronary artery aneurysms, thrombosis and myocardial infarction. Although rare, Kawasaki disease is the most common cause for childhood myocardial infarction.

**Small vessel vasculitis**

Small vessel vasculitis is characterized by the involvement of vessels smaller than arteries, that is, involvement of capillaries, venules or arterioles. Arteries also may be
involved, but all forms of small vessel vasculitis affect predominantly vessels other than arteries, and in many patients arteries are not involved at all. The frequency of arterial involvement varies among different vasculitides. For example, arterial involvement is extremely rare in Henoch–Schönlein purpura or cryoglobulinaemic vasculitis, whereas it is frequent in GPA, MPA and EGPA. Of the many variants of small vessel vasculitis, some of which are listed in Table 9.1, this chapter will focus on the diagnostic categorization of GPA, MPA and EGPA, Henoch–Schönlein purpura and cryoglobulinaemic vasculitis. More details about the clinical manifestations and treatment of these and other vasculitides can be found in other chapters of this book.

Granulomatosis with polyangiitis (Wegeners granulomatosis) (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA)

GPA, MPA and EGPA once were considered variants of polyarteritis nodosa because they often have necrotizing arteritis as a component of the vasculitic process (Figure 9.2c).** Heinz Klinger and Friedrich Wegener recognized what they considered to be a variant of polyarteritis nodosa that had destructive necrotizing inflammation that often affected the upper and lower respiratory tract. In 1954, Gabriel Godman and Jacob Churg described in more detail the full spectrum of pathological and clinical features what was then called ‘Wegener’s granulomatosis’. These features include necrotizing ‘angiitis’, necrotizing granulomatous inflammation of the respiratory tract and necrotizing glomerulonephritis (Fig. 9.2d). Patients with limited expressions of GPA also occur, for example, patients with disease confined to the respiratory tract.

Recently there has been substantial controversy over the use of the eponym ‘Wegener’s granulomatosis’ because of evidence that Friedrich Wegener was an active member of the Nazi party during World War II.** As a consequence, the alternative name ‘granulomatosis with polyangiitis’ (GPA) has been proposed to replace Wegener’s granulomatosis. Time will tell whether this change in nomenclature will become widely adopted.

Jacob Churg and Lotte Strauss described another variant of necrotizing vasculitis in 1951 characterized by ‘allergic granulomatosis, allergic angiitis and periarteritis nodosa’. These patients also had asthma, blood eosinophilia and necrotizing glomerulonephritis. This variant of necrotizing vasculitis is often called Churg–Strauss syndrome.

In their classic 1954 article that definitively described GPA, Godman and Churg also concluded that GPA and allergic granulomatosis (EGPA) are closely related to each other, and both also are closely related to what they called ‘microscopic periarteritis’. They further concluded that GPA, EGPA and microscopic periarteritis (which is now usually called MPA) are distinct from polyarteritis nodosa. These conclusions are supported by the frequent finding of ANCA in patients with GPA, MPA, and EGPA, but not polyarteritis nodosa (as defined by the CHCC Nomenclature System).

Thus, ANCA are a useful diagnostic serological marker for MPA, GPA and EGPA. However, a positive ANCA result is not absolutely specific or sensitive, and thus must be interpreted in light of the other data. Approximately 80–90% of active
untreated GPA or MPA patients, and approximately 40% of EGPA patients are ANCA positive, although this increases to 75% if glomerulonephritis is present. ANCA in patients with vasculitis or glomerulonephritis are specific for proteins in the cytoplasmic granules of neutrophils and the lysosomes of monocytes. The two major types of ANCA cause two staining patterns, cytoplasmic (C-ANCA) and perinuclear (P-ANCA), when they are detected using indirect immunofluorescence microscopy. The P-ANCA pattern is an artefact of substrate preparation that results in redistribution of the antigen from cytoplasm to nucleus during substrate preparation. Enzyme immunoassay (EIA) reveals that most C-ANCA have specificity for proteinase 3 (PR3-ANCA) and most P-ANCA have specificity for myeloperoxidase (MPO-ANCA).

In North America and Europe, patients with GPA usually have C-ANCA (PR3-ANCA), patients with MPA have slightly more P-ANCA (MPO-ANCA) than C-ANCA (PR3-ANCA) and patients with EGPA have predominantly P-ANCA (MPO-ANCA). In Asia, MPO-ANCA is much more prevalent than PR3-ANCA in all clinicopathological variants of ANCA disease.

Patients with GPA, MPA and EGPA can be classified by these clinicopathological features as well as by their serological status, that is PC3-ANCA positive, MPO-ANCA positive or ANCA negative. Perhaps the most informative approach is to use both approaches, for example MPO-ANCA positive MPA or ANCA negative MPA.

### Henoch–Schönlein purpura (IgA vasculitis)

In the 1800s, Johann Schönlein and Eduard Henoch reported the association of purpura with arthralgias, arthritis, abdominal pain and nephritis. In the early 1900s, this syndrome was called ‘Henoch’s purpura’, and more recently ‘Schönlein–Henoch purpura’ or ‘Henoch–Schönlein purpura’. CHCC 2011 recommends using the term IgA vasculitis to emphasize the IgA-dominant immune deposits.

Many variants of small vessel vasculitis can produce the syndrome described by Henoch and Schönlein. For example, cryoglobulinaemic vasculitis, GPA, EGPA, MPA, lupus vasculitis, rheumatoid vasculitis and serum sickness vasculitis all can manifest purpura, abdominal pain, arthralgias and nephritis. Thus, the term Henoch–Schönlein purpura has little specific value in patient management unless it is confined to a more restricted group of patients who have similar and predictable natural histories and appropriate therapy. Fortunately, advances in immunopathology and serology have provided a number of tools for differentiating among clinically and histologically indistinguishable categories of small vessel vasculitis. This has resulted in refining the definitions of a number of diagnostic terms, including Henoch–Schönlein purpura, Goodpasture’s syndrome, MPA and polyarteritis nodosa.

The advent of immunofluorescence microscopy allowed the identification of deposits of immunoglobulins and complement within vessel walls of patients with certain types of vasculitis. Examination of patients with Henoch–Schönlein purpura revealed a distinct group, often children, who had IgA-dominant immune deposits in the walls of vessels. This distinguished these patients from patients with other types of vascular immune deposits, such as patients with cryoglobulinaemic vasculitis who have
granular vascular deposits of IgM and IgG, and from patient with little or no vascular immunoglobulin localization, such as patients with GPA, MPA and EGPA. As mentioned earlier, these latter patients with so-called pauci-immune small vessel vasculitis usually have a relatively specific serological marker, that is ANCA.

By the CHCC approaches to diagnostic categorization, a patient with signs and symptoms of small vessel vasculitis who has IgA-dominant vascular immune deposits should be diagnosed as Henoch–Schönlein purpura (IgA vasculitis), whereas a patient with the same clinical presentation who has circulating cryoglobulins and vascular cryoglobulin deposits should be diagnosed as cryoglobulinaemic vasculitis, and a patient with the same clinical presentation who has no vascular immune deposits but has circulating ANCA should be diagnosed as MPA. A caveat to this last diagnosis is whether or not there is evidence for granulomatous inflammation or asthma. If there is granulomatous inflammation and no asthma, the proper diagnosis is GPA. If there is asthma and eosinophilia, the proper diagnosis is EGPA.

Cryoglobulinaemic vasculitis

Cryoglobulinaemic vasculitis is caused by cryoglobulins that localize in small vessel walls and incite inflammation. Purpura, arthralgias and nephritis are the most common manifestations. Cryoglobulinaemic vasculitis must be differentiated from other small vessel vasculitides that cause the same signs and symptoms of small vessel disease. For example, Henoch–Schönlein purpura and MPA also frequently cause purpura, arthralgias and nephritis. Useful although not completely specific diagnostic markers for cryoglobulinaemic vasculitis include mixed cryoglobulinaemia, rheumatoid factor activity and laboratory evidence for hepatitis C virus infection. Very low serum C4 with normal or slightly low C3 is a characteristic abnormality. IgA-dominant immune deposits in vessels, for example in skin or kidney biopsy specimens, indicate Henoch–Schönlein purpura rather than cryoglobulinaemic vasculitis. Positive serological testing for ANCA suggests a pauci-immune small vessel vasculitis, such as GPA or MPA, rather than cryoglobulinaemic vasculitis.

Take home points

1. Because many different vasculitides can produce indistinguishable features, one should be cautious not to rush to conclusions based on the first bits of evidence. For example, purpura with nephritis in a child is most likely Henoch–Schönlein purpura (IgA vasculitis), but could be microscopic polyangiitis, cryoglobulinaemic vasculitis or other small vessel vasculitides.

2. Diagnostic categorization of vasculitis is a complex process that requires knowledgeable integration of clinical, laboratory and pathological data. For example, serological testing for autoimmune and infectious diseases often provides useful data.

3. Carefully consider not only what features are present, but also, equally important, what features are absent. For example, both the presence and the absence of hypocomplementaemia, cryoglobulins, ANCA, blood eosinophilia, hepatitis antibodies and
other laboratory abnormalities allows narrowing of the differential diagnosis in a patient with evidence for systemic vasculitis.

References

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest

** Classification recommendations of the Chapel Hill Consensus Conference that currently is the most widely used approach although a revised 2011 version of the CHCC will replace the 1993 version.

* Modification and extension of the Chapel Hill Consensus Conference classification for childhood vasculitis.

3. Savory W.S. (1856) Case of a young woman in whom the main arteries of both upper extremities and of the left side of the neck were throughout completely obliterated. *Med Chir Trans Lond* 39, 205–219.


** A review of the differential diagnosis of small vessel vasculitis placed in the historical context of the classification of vasculitis in general.

* Excellent description of the clinical features of polyarteritis nodosa and Churg–Strauss syndrome.


* Description of several important systemic vasculitides in children.


* Explanation for the recommendation by multiple professional societies that the name Wegener’s granulomatosis be replaced by the term granulomatosis with polyangiitis.


Chapter 10

The immunopathogenesis of vasculitis

Andrew McClean and C.O.S. Savage

Introduction

Vasculitis comprises a group of diseases characterized by necrotizing inflammation of blood vessel walls. However, the diseases included under this umbrella term vary widely in immunopathogenic mechanisms, clinical presentation and pathology. Classification has therefore proved to be problematic, but vasculitis is commonly divided into subgroups of diseases according to the size of the smallest vessels affected. In 1994, the ‘Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis’ noted the clinical utility of subdividing the small vessel vasculitides into those associated with the presence of anti-neutrophil cytoplasmic antibody (ANCA), and those not. ANCA-associated vasculitis (AAV) comprises Wegener’s granulomatosis, microscopic polyangiitis and Churg–Strauss syndrome.

The prognosis from AAV has improved dramatically over the last 30 years, from a survival rate of only 20% at 1 year, to around 80% at 5 years, but it remains an incurable disease. In many cases, treatment simply converts it from a rapidly fatal illness into a disease with a chronic relapsing remitting course, associated with considerable chronic organ damage and impaired quality of life. Understanding the mechanisms of immunopathogenesis will be vital for the development of more effective treatments for AAV. Over the last decade in particular there have been huge advances in our understanding, and it is hoped that current work, both in vitro and utilizing improved animal models, will translate into further breakthroughs in therapy.

ANCA

ANCA are IgG autoantibodies directed against specific lysosomal constituents of neutrophils. They were first identified as recently as 1982, in a group of patients with segmental necrotizing glomerulonephritis. The investigators discovered what is now known as c-ANCA, that is, ANCA that shows diffuse cytoplasmic staining of ethanol-fixed neutrophils on indirect immunofluorescence.

In 1988, Falk and Jennette identified that there were two different patterns of staining: in addition to c-ANCA, they described ANCA showing an artefactual perinuclear staining pattern now referred to as p-ANCA. Using the technique of enzyme-linked immunosorbent assay (ELISA), they discovered that p-ANCA is usually directed
against the antigen myeloperoxidase (MPO).\textsuperscript{3} We now also know that c-ANCA is normally directed against proteinase 3 (PR3).

MPO is a 150 kDa chloride peroxidase, which in health is used by the neutrophil to kill phagocytosed bacteria; during the ‘respiratory burst’, it catalyses the formation of hypochlorous acid (HOCl) from hydrogen peroxide (H$_2$O$_2$) and chloride ions. The natural inhibitor of MPO is caeruloplasmin. PR3 is a 29 kDa serine protease with a host of functions, including modulation of inflammatory mediators (for example, the cleavage of interleukin (IL)-8).\textsuperscript{4} The natural inhibitor of PR3 is $\alpha$1-antitrypsin. MPO and PR3 are both lysosomal enzymes, and are most abundant in the cytoplasmic primary granules of neutrophils and monocytes. Despite being present in the cytoplasm, MPO is not normally found on the cell membranes of resting neutrophils, but rather only on the membranes of neutrophils that have been ‘primed’, as we will discuss later. On the other hand, PR3 membrane expression is bimodal on resting neutrophils; that is, resting neutrophils may be divided into subsets with either low or high membrane expression even in healthy subjects. PR3 membrane expression patterns are stable for an individual, and twin studies suggest that the level of membrane expression is genetically determined.\textsuperscript{5}

The association between ANCA and AAV is extremely strong, with antibodies against PR3 being very closely associated with Wegener’s granulomatosis, and those against MPO being associated with microscopic polyangiitis and Churg–Strauss syndrome. However, around 10\% of people with AAV will have no detectable ANCA in their sera by either indirect immunofluorescence or ELISA. Also, ANCA has been found in the sera of patients with other autoimmune diseases, inflammatory bowel disease and infections such as tuberculosis, although in those diseases the ANCA is not usually directed against MPO or PR3. ANCA testing must be taken in clinical context: when the clinical suspicion is very low, the negative predictive value of combined ANCA testing by immunofluorescence and ELISA is 99\%; when the clinical suspicion is very high, the positive predictive value is 95\%.\textsuperscript{6}

Is AAV an autoimmune disease?

Much debate has surrounded the nature of ANCA: is it actually pathogenic, or merely a marker of disease? After all, the pathology found on renal biopsy of AAV is described as ‘pauci-immune’. This is in sharp contrast to anti-glomerular basement membrane (GBM) disease, where pathogenic antibodies to type IV collagen in the GBM cause striking immune complex deposition on biopsy. Although debate is still ongoing, the research done since 1990, when ANCA was first shown \textit{in vitro} to induce respiratory burst and degranulation,\textsuperscript{7} has provided fairly compelling evidence that the disease is autoimmune, and that ANCA is indeed pathogenic.

The strongest direct evidence is the case report of the baby born of a mother with active AAV, who developed a pulmonary-renal syndrome 48 hours after delivery.\textsuperscript{8} The baby was found to have comparable levels of anti-MPO ANCA to its mother, presumably due to transplacental transfer, and recovered following treatment with steroids and plasma exchange. The other evidence may be divided into circumstantial evidence, evidence from \textit{in vitro} experiments, and that from animal models.
Circumstantial evidence
There is an association between ANCA titre and disease activity in humans—often a rise in anti-PR3 or anti-MPO ANCA titre may herald a flare in the disease. However, it must be pointed out that some sufferers will demonstrate consistently high ANCA levels without clinically active disease, and conversely that some flares will occur without a rise in titre. Supportive evidence also comes from the MEPEX trial, which showed that patients with severe AAV had a lower risk of being dialysis-dependent at 12 months if they were treated with plasma exchange instead of methylprednisolone. Plasma exchange is a treatment that would be expected to remove circulating immunoglobulin (Ig)G from the blood, although of course it could have other effects such as altering cytokine levels.

In vitro evidence
The first in vitro evidence for the pathogenicity of ANCA was the demonstration that ANCA could induce respiratory burst and degranulation. It has also been shown that ANCA can cause neutrophils to release a number of cytokines and chemokines, including IL-1, IL-8 and tumour necrosis factor (TNF)-α. Other studies have shown that damage occurs to endothelial cells when incubated with neutrophils and ANCA, and yet another has shown that ANCA may cause accelerated and dysregulated neutrophil apoptosis in vitro. All of these studies and more have demonstrated in vitro that ANCA are capable of inducing neutrophil-mediated inflammation and endothelial damage, but the evidence that has recently been provided by animal models is perhaps even more compelling.

Animal models
Early animal models were flawed either because they injected a combination of ANCA and anti-GBM antibody, making causal inference difficult, or because they produced marked immune complex deposition, in clear contrast to human AAV. The first convincing animal work was carried out on mice by Xiao and colleagues in 2002. They immunized MPO knockout mice with mouse MPO, to induce production of anti-MPO antibodies. They then injected splenocytes from those mice into a mouse model known as Rag2 (-/-), which lacks functioning T and B lymphocytes. This essentially introduced anti-MPO T and B lymphocytes, and caused a dose-dependent anti-MPO IgG ANCA production in the Rag-2 (-/-) mice. All mice that received splenocytes developed mild to moderate glomerular immune deposits, and those mice that received the highest doses developed a severe necrotizing and crescentic glomerulonephritis, as well as haemorrhagic pulmonary capillaritis and some granuloma formation.

They then tested the ability of ANCA alone to produce such effects, by injecting purified anti-MPO IgG ANCA into Rag2 (-/-) and wild-type mice. They found that both strains developed focal necrotizing and crescentic glomerulonephritis without immune complex deposition. Their conclusion was therefore that anti-MPO IgG ANCA was able to produce a pauci-immune necrotizing crescentic glomerulonephritis, both in the setting of absent lymphocytes, and also in that of an intact immune system. It is noteworthy that the glomerulonephritis induced by the injection of splenocytes...
was more severe than that induced by injection of ANCA alone, suggesting that lymphocytes may contribute something else to the process beyond merely the production of ANCA (as discussed further later in this chapter).

A rat model of anti-MPO ANCA has been developed by Little and colleagues. They injected human MPO into Wistar/Kyoto (WKY) rats, which then produced anti-MPO antibodies that cross-reacted against rat neutrophils. The rats developed experimental autoimmune vasculitis (EAV), comprising pauci-immune crescentic glomerulonephritis and lung haemorrhage. What makes this model even more interesting is that they also used a technique known as intravital microscopy to demonstrate \textit{in vivo} that the ANCA conferred enhanced adhesion of neutrophils to the endothelial wall, as well as transmigration across the endothelium. Experiments by Nolan and colleagues on a mouse model also demonstrated evidence of enhanced leucocyte–endothelial cell interactions in the presence of anti-MPO IgG.

Kain and her group used animal models in their investigation of a different type of ANCA, directed against the antigen hLAMP-2, a heavily glycosylated type 1 membrane protein that is found on human neutrophil lysosomal membranes and the neutrophil surface membrane. They propose that this new ANCA is even more prevalent in human AAV than MPO and PR3 (93% in their cohort), and that it has the ability to directly induce endothelial damage in the absence of neutrophils. In one of their experiments, they injected WKY rats with rabbit anti-LAMP-2 antibodies. At 2 hours, rabbit IgG was identifiable bound to glomerular capillaries, but after 24 hours the rats had developed a focal necrotizing glomerulonephritis and the IgG deposits were no longer detectable.

\textbf{Why is tolerance lost?}

The evidence discussed provides a strong case that AAV is an autoimmune disease, but the question then arises: why do patients lose their tolerance of MPO and PR3? The answer remains uncertain, but there are some attractive theories based on existing evidence.

A number of genetic factors are associated with an increased incidence of AAV. As mentioned previously, a variable proportion of human neutrophils express high levels of PR3 on their surface membrane in the resting state. This has been shown to have a genetic basis, and an association has been demonstrated between higher levels of surface expression and the risk of AAV. Studies by Kamesh and colleagues showed evidence that cytotoxic T lymphocyte antigen (CTLA)-4, a susceptibility locus for a number of common autoimmune diseases, may also be involved in the development of AAV. Other pointers to genetic predisposition include the increased expression of C3F and C4A3 complement gene polymorphisms in patients with AAV, and the massively increased frequency of \(\alpha_1\) antitrypsin defects in patients with Wegener’s. Such defects confer a worse prognosis, which is perhaps unsurprising given that \(\alpha_1\) antitrypsin normally inhibits PR3.

The most common environmental factor linked with the development of AAV is exposure to silica. The precise reason for this is unknown as yet, but there are several possibilities. One is that silica could cause production of ANCA, because it is a potent
stimulator of T and B lymphocytes. It is also known that silica exposure can cause release of PR3 and MPO, and that it causes accelerated apoptosis. It is theorized that disordered apoptosis, whether due to silica exposure or otherwise, could result in cross-presentation of self-antigens by dendritic cells (reviewed in \cite{21}).

Infection is also commonly suggested as a reason for loss of self-tolerance in AAV. There is evidence linking chronic nasal carriage of *Staphylococcus aureus* to increased relapse rates in Wegener’s granulomatosis,\cite{22} leading to the suggestion that sufferers should remain on long term co-trimoxazole therapy. Indeed, there is evidence that such therapy does reduce relapse rates.\cite{23} A theory that could explain this link with infection was put forth by Pendergraft and colleagues.\cite{24} They observed that many of their patients had antibodies not only to PR3, but also to a protein they termed complimentary PR3 (cPR3), a peptide translated from the anti-sense strand of the DNA encoding PR3. They also found that the antibodies to PR3 and cPR3 can bind to each other, indicating they may have an idiotypic relationship. They tested this theory by immunizing mice with cPR3, and indeed they found that antibodies were produced not only to cPR3, but also to PR3 itself. Both *Staphylococcus aureus* and *Entamoeba histolytica* have been found to express proteins mimicking cPR3, so they could potentially be an exogenous stimulus for anti-PR3 ANCA production.

Although it has yet to be replicated by other groups, the work of Kain and colleagues on anti-hLAMP-2 ANCA provides us with another intriguing theory.\cite{16} They have identified two epitopes on the protein backbone of hLAMP-2 commonly recognized by ANCA. They note that one of the epitopes has 100% homology to the bacterial protein FimH, located on the tip of type-1 fimbriae of gram negative bacteria such as *Escherichia coli*, *Klebsiella* or *Proteus*. Interestingly, the anti-hLAMP-2 ANCA will also cross-react with FimH. Their hypothesis is that infection with FimH-expressing bacteria leads to development of cross-reacting antibodies, triggering autoimmunity to hLAMP-2 and a resultant pauci-immune focal necrotizing glomerulonephritis.

It is well established that many drugs can cause the development of ANCA, most classically propylthiouracil (PTU). The clinical manifestations of drug-induced AAV are similar to those of idiopathic AAV, but there are significant differences. For example, the ANCA found usually demonstrates multi-antigenicity, and the diagnosis is made by excluding other medical conditions and linking the temporal onset of disease to use of the offending drug. Treatment also differs: removal of the drug is most important, and immunosuppression is much less key than in idiopathic disease (reviewed in \cite{25}).

**The mechanism of disease pathogenesis**

Current evidence suggests that there are four basic steps in the immunopathogenesis of AAV:

1. both the neutrophil and the endothelium must be ‘primed’ in order for the process to begin;
2. the primed neutrophil adheres to the endothelium;
3. ANCA interacts with the adhered neutrophil, leading to neutrophil activation;
4. neutrophil activation results in damage to the endothelium.
This is an oversimplification of the situation as it is in vivo, but it provides us with a framework for looking at the process (Fig. 10.1).

**Neutrophil priming**

As described previously, there is normally no MPO on the surface of neutrophils, and the surface expression of PR3 varies considerably between individuals. In order therefore for effective interaction to occur between ANCA and antigen, the neutrophils must be ‘primed’ in such a way that they carry PR3 or MPO on their cell surface. It is believed that this is brought about by the action of cytokines, particularly TNF-α and IL-1. In vitro and animal experiments suggest that TNF-α is central to neutrophil priming, and in some animal models it has been shown that anti-TNF-α therapy will arrest glomerular crescent formation and pulmonary haemorrhage. Unfortunately, such treatments have been disappointing in humans, perhaps because...
IL-18 can fulfil the roles normally carried out by TNF-α, and is widely expressed in AAV lesions.28

**Activation of the endothelium, and neutrophil adhesion**

There is *in vitro* evidence that adherence to the endothelium is a prerequisite for neutrophil activation.29 However, without stimulation by cytokines, glomerular endothelium does not support neutrophil adhesion because it does not normally express P and E selectin on its surface. Once selectin expression has been induced by cytokines such as IL-1 and TNF-α,30 the neutrophil begins to roll on the surface of the endothelium. A second signal, such as ANCA, causes a conformational change in β2-integrin on the neutrophil surface. This allows the neutrophil to stop rolling and to adhere firmly to, and even transmigrate through, the endothelium. Some studies previously suggested that ANCA might have a direct affect on the endothelium as well, but it has not been possible to replicate this work.

**ANCA activation of the neutrophil**

Antibodies normally bind to their target antigen by their F(ab)2 portion, and then bind to the Fc-γ receptor on the neutrophil via their Fc portion, thereby helping the neutrophil to phagocytose the target antigen and release cytotoxins in the vicinity. This situation is uniquely different in the case of ANCA, as the target antigen (usually PR3 or MPO) is also on the surface membrane of the neutrophil. In the case of ANCA binding, the antibody binds to neutrophils by both the F(ab)2 and the Fc fragments, and both are required for effective neutrophil activation.

Once activated by ANCA, neutrophils undergo several changes, including the increased expression and altered conformation of β2-integrins. This has been demonstrated *in vitro*, where neutrophils flowing over an endothelial monolayer are induced by incubation with ANCA to stop rolling and adhere firmly to the monolayer; this also results in a 10-fold increase in neutrophil transmigration.31 As discussed previously, Little and colleagues have used intravital microscopy to demonstrate this phenomenon *in vivo*.14 ANCA also induces polymerization of the actin cytoskeleton within the neutrophil, making the cell more rigid. It has been suggested that this could lead to sequestration within capillary beds, potentially explaining why AAV tends to mainly affect regions with major capillary beds, such as the kidneys and lungs.32

Activated neutrophils also secrete further cytokines, including TNF-α and IL-1, as well as the chemokine IL-8, monocyte chemoattractant protein 1 and leukotrine-B4.10,33 These substances act as chemoattractants for further neutrophils, as well as monocytes and lymphocytes, resulting in perpetuation of unregulated inflammation and damage.34

Apoptosis is dysfunctional in neutrophils that have been activated by ANCA. There is a delay in the expression of apoptotic surface molecules required for effective phagocytosis by macrophages. This therefore delays their removal from the tissues by macrophages, resulting in secondary necrosis, the release of damaging intracellular contents and yet more spiralling inflammation.21

Studies suggest that the main epitopes on PR3 recognized by anti-PR3 ANCA are situated close to the catalytic site.35 This causes ANCA to inhibit binding of the natural
inhibitor of PR3, α1 antitrypsin, resulting in unregulated protease activity. Interestingly, it has been reported that the affinity of anti-PR3 ANCA for its antigen varies with disease activity, being much stronger during times of active disease than during remission. As a result, those who are in remission have much more effective inhibition of PR3 activity. Although anti-MPO ANCA can similarly inhibit the binding of caeruloplasmin to MPO, the clinical effect of this is less clear.

Damage to the endothelium results in the classical histopathology of AAV

When primed neutrophils are incubated together in vitro with ANCA and endothelial cells, endothelial damage results. Ultrastructural studies also illustrate that in vivo, the earliest tissue damage seen in AAV is the swelling and necrosis of endothelial cells. As the process spirals out of control, detachment of the endothelium from its basement membrane occurs, the exposed basement membrane initiates thrombosis in the capillary lumen and that in turn results in segmental necrosis of the glomerulus. If the segmental necrosis causes vessel rupture, bleeding into Bowman’s space causes epithelial cells and monocytes to form the characteristic crescentic scar.

There are two main mechanisms by which ANCA-activated neutrophils may cause such damage to endothelium: once they are firmly adhered to endothelium and activated by ANCA, they undergo respiratory burst to produce superoxide and other reactive oxygen species, and they also degranulate to release MPO, PR3 and the other proteolytic constituents of their primary granules into the microenvironment. We do not yet understand the mechanism through which neutrophil activation by ANCA brings about degranulation, but the pathway leading to respiratory burst is quite well delineated. Once the unique binding of ANCA by both the Fc and F(ab)2 fragments has occurred, two separate intracellular signalling cascades are set in motion: the F(ab)2 fragment activates inhibitory G proteins, whereas binding of the Fc fragment to the Fc-γ receptor is responsible for activating intracellular tyrosine kinases such as Syk kinase. Both cascades then converge on the GTPase p21ras. The tyrosine kinases activated by Fc-γ receptor binding are thought to induce respiratory burst through activation of NADH oxidase, but both signalling pathways must be engaged to cause a respiratory burst, as they are both required for full activation of p21ras. Transient increased p21ras activity precedes the rise in superoxide production seen during respiratory burst.

Is the observed endothelial damage primarily a result of the respiratory burst, or is it more likely secondary to neutrophil degranulation? It appears that the release of toxic primary granules is probably the most important cause, because there is evidence that endothelial cells may have the ability to inhibit the respiratory burst of activated neutrophils by suppressing NADPH oxidase activity. In vitro studies suggest that degranulation may cause damage through internalization of PR3, elastase and MPO by endothelial cells. Once internalized, PR3 can cause damage by cleaving p21waf, thereby inducing endothelial cell apoptosis. Likewise, MPO may be internalized and then damage the endothelial cells by intracellular generation of active oxygen species.
The complement cascade in AAV

Traditionally it has been thought that the complement system is not involved in AAV, for two reasons: because the histology is ‘pauci-immune’, and because serum complement levels are normal despite active disease. However, both of these arguments are flawed.

First, IgG is also rarely found on biopsy in AAV, even though it is central to the whole disease process. Also, several pathology studies in AAV have shown a degree of immune complex deposition, both in skin biopsies and also in early renal biopsies. C3, and to a lesser extent C1q have both been shown. Second, hypocomplementaemia is a very insensitive way of measuring complement consumption; anti-GBM disease, for example, features extensive complement deposition but normal serum complement levels.

Positive evidence of complement involvement in AAV has been found in both in vitro and in vivo experiments. In vitro experiments have suggested that the oxygen radicals, MPO and various proteases released by ANCA-activated neutrophils are all capable of activating the complement system. Mouse studies have shown that the alternative pathway of the complement system appears to be critical to the model of anti-MPO ANCA-induced crescentic glomerulonephritis. Finally, in humans it has been found that there is skewed expression of certain gene polymorphisms: increased C3F expression was found among people who were PR3-ANCA positive, and increased expression of C4A3 was found in AAV as a whole, although the clinical relevance is not clear (reviewed in).

What is the role of lymphocytes?

The role of B lymphocytes and plasma cells in AAV is obviously critical, as there is now convincing evidence that the ANCA they produce is central to the disease immunopathogenesis. This has been illustrated in recent years by the success of rituximab in controlling resistant disease. Rituximab is a chimeric antibody directed against the CD20 antigen on B cells, and it has been shown to induce remission in disease refractory to corticosteroid and cyclophosphamide therapy.

Culton and colleagues have demonstrated that the surface expression of CD19 in AAV is 20% lower than on the B cells of healthy controls. This antigen is involved in signal transduction, and the authors propose that the lower CD19 expression results in lower levels of signal transduction, perhaps allowing autoreactive B cells to avoid being selected out.

T lymphocytes probably have a significant role to play as well. As ANCA are high-affinity, class-switched antibodies, it is likely that CD4+ T cell help is required. Further evidence of their involvement comes from the high numbers of T cells found in renal biopsy specimens; they are a major feature of the interstitial infiltrate, and their numbers correlate with the number of crescentic glomeruli and the serum creatinine level.

There are many changes within the circulating T cell populations in AAV. Often up to 20% are found to be activated, even during remission. Lymphopaenia and markedly low numbers of CD4+ T cells have been found even in untreated patients, suggesting that it is secondary to the disease itself rather than to therapy. There is skewing towards
effector memory cells, which could be a reason for the common relapsing remitting course, and could be a target for new therapies (reviewed in\textsuperscript{55}).

**Monocytes in AAV**

In the same way that neutrophils do, monocytes from the peripheral blood of patients with AAV express MPO and PR3 on their surface during periods of active disease. *In vitro*, ANCA has been shown to activate monocytes, causing the release of IL-8,\textsuperscript{56} a potent attractor for neutrophils, and monocyte chemoattractant protein-1.\textsuperscript{57} It even causes monocytes to release reactive oxygen species.\textsuperscript{58}

As discussed previously, macrophages are responsible for removing apoptotic neutrophils, but the process of neutrophil apoptosis is disturbed by ANCA activation. When these activated neutrophils are eventually ingested, the ingesting macrophages display enhanced phagocytotic activity and TNF-\(\alpha\) release.\textsuperscript{59}

**Take home points**

1. AAV is now considered an autoimmune disease, with ANCA having a pathogenic role.
2. As an autoimmune disease, the development of AAV must involve some loss of tolerance. This may result from genetic factors, environmental factors such as silica exposure, or perhaps as a result of an infective antigen that mimics endogenous antigen.
3. The primary target for injury in AAV is the endothelial cell, probably as a result of injury by PR3, MPO or elastase.
4. Although ANCA exerts its effects via neutrophil activation, there is growing evidence that monocytes, lymphocytes and the alternate pathway of the complement system are all intimately involved in the immunopathogenesis of AAV.
5. Our improving understanding of the immunopathogenesis of AAV is opening up possible new avenues for therapy, such as targeting of intracellular signalling.

**References**

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest

REFERENCES

* Subgroup analysis of data from the MEPEX trial, investigating the efficacy of plasma exchange as adjunctive therapy in dialysis-dependent AAV patients.
** Important early animal work, creating a mouse model which closely mimics human AAV.
* Novel animal work that allowed in vivo study of the effects of ANCA.
* Use of intravital microscopy to investigate the role of cytokines and ANCA in AAV.
* Interesting work which describes what may be a new ANCA, as well as suggesting a possible link between infection and AAV, and also a possible mechanism for the loss of tolerance.


* Thorough review of the pathogenicity, detection and clinical usefulness of ANCA.


* Randomized controlled study investigating the efficacy of co-trimoxazole in preventing relapses of Wegener’s granulomatosis in remission.


** Offers an intriguing possible explanation for the loss of tolerance in AAV.


* Comprehensive review of T lymphocytes in Wegener’s granulomatosis.


Chapter 11

Pathology of vasculitis: Wegener’s granulomatosis, microscopic polyangiitis, renal limited vasculitis, and Churg–Strauss syndrome

Franco Ferrario and Maria Pia Rastaldi

A pauci-immune necrotizing crescentic glomerulonephritis is the morphological hallmark of anti-neutrophil cytoplasm antibodies (ANCA)-associated microscopic vasculitis.\textsuperscript{1,2} The lesion can widely vary as far as degree and extent, and characterizes fundamentally Wegener’s granulomatosis, microscopic polyarteritis and its renal limited variant. Although less common, Churg–Strauss syndrome belongs to the same group of ANCA-related small vessels vasculitis, and shows a similar renal involvement, in which the presence of eosinophil infiltration can be a distinguishing feature, but its absence does not exclude the diagnosis.\textsuperscript{3}

Considering our experience with the review of 231 cases for the Italian Renal Immunopathology Group, of 173 biopsies for the EUVAS group,\textsuperscript{4,5} and our recent revision of 88 biopsies of ANCA-associated renal vasculitis performed from 1990 to 2008 at the Department of Nephrology of Milan Policlinic, we can confidently state that there is not a statistical difference in quality and extent of morphological lesions in the kidneys among the different types of ANCA-associated vasculitis (Table 11.1). It follows that, for instance, the presence of peri-glomerular granulomas cannot be considered exclusive of Wegener’s granulomatosis, because they are also present in some cases of renal limited vasculitis. On the contrary, true interstitial granulomas, albeit rare and difficult to identify when the underlying structure is not recognizable, probably constitute the unique morphological distinguishing finding for Wegener’s granulomatosis.\textsuperscript{5,6} With these premises, the four entities will be described here as a whole.

Renal biopsy remains a fundamental instrument for diagnosis and particularly for the management of these disease entities, because the degree of clinical symptoms is frequently unrelated to the level and the activity of renal lesions.\textsuperscript{7–9} Microscopic features of diffuse necrotizing crescentic glomerulonephritis can be detected in subjects with urinary abnormalities or mild renal failure; furthermore, the highest levels of serum creatinine mostly correspond to histological pictures where sclerosis predominates.
Table 11.1  Main histological features in ANCA-associated renal vasculitis, according to our experience in 117 case study for the EUVAS group

<table>
<thead>
<tr>
<th>Diagnosis (no cases)</th>
<th>Necrosis &lt;30%</th>
<th>Necrosis &gt;60%</th>
<th>Crescents &lt;30%</th>
<th>Crescents &gt;60%</th>
<th>Periglomerular Infiltrates (+/++)</th>
<th>Periglomerular granulomas</th>
<th>Renal arteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>WG* (51)</td>
<td>68%</td>
<td>9%</td>
<td>51%</td>
<td>32%</td>
<td>34%</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>MPA* (48)</td>
<td>76%</td>
<td>16%</td>
<td>31%</td>
<td>32%</td>
<td>39%</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>RLV* (18)</td>
<td>82%</td>
<td>12%</td>
<td>22%</td>
<td>45%</td>
<td>45%</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Results are expressed as percentages

*WG= Wegener’s granulomatosis
*MPA= Micropolyarteritis
*RLV= Renal limited vasculitis
Since the discovery of ANCA tests and their prevalent association with these forms, diagnosis has greatly improved, and renal involvement is now often detected before the creatinine starts to rise. In 1994, their classification was then defined by the Chapel Hill consensus conference and an international agreement on nomenclature was reached. One of the major goals was the differentiation between classic polyarteritis nodosa (PAN) and microscopic polyangiitis (MPA), as defined by the presence of capillary necrosis in MPA, whereas the involvement of medium size vessels is common to both entities.

It is well known that in kidney biopsies an identifiable angiitis of small and medium size vessels is present in a relatively small number of specimens, with a reported frequency ranging from 10% to 30% (12% in the EUVAS group experience) and was found in two out of 19 cases of Churg–Strauss syndrome by Clutterbuck et al. Vasculitis is defined by the presence of necrotizing inflammation involving one or more layers of the vessel wall. Leucocyte infiltration is always present, sometimes massive, with a possible picture of granulomatous lesion, containing also epithelioid cells and giant cells. Eosinophils can be strikingly predominant in Churg–Strauss syndrome, but their absence or scarcity cannot exclude the diagnosis, that has always to be performed associating clinical and histological criteria.

We can then assert that in the kidney, by light microscopy, necrotizing crescentic damage of the glomerular tuft is the characterizing lesion of these forms. Isolated necrosis of the tuft has been found in our recent revision in 7–9% of cases and is probably expression of early damage, whereas the most common finding is the association of necrosis with extracapillary proliferation. Both necrosis and extracapillary proliferation can involve the tissue in a focal and segmental or global and diffuse way, sometimes leaving no intact glomeruli and giving a picture of a very severely injured kidney.

It is important, especially for differential diagnosis, to focus on the concept that not only glomeruli not involved by necrotizing extracapillary damage, but also the remaining undamaged parts of the tuft in glomeruli with capillaritis, are quite normal, without the appearance of intracapillary proliferative lesions and matrix expansion, nor the presence of glomerular basement membrane alterations.

In damaged glomeruli and around them, a characteristic leucocyte accumulation is generally present, sometimes massive, and associated with rupture of the Bowman’s capsule, making it impossible to discriminate between intra-glomerular and extra-glomerular events and giving to these areas a typical picture of peri-glomerular granulomatous lesion.

Although the origin of epithelial cells present in the crescents still remains an issue under discussion, the prevailing contribution of leucocytes to extracapillary lesions in renal vasculitis has been largely documented by numerous investigators, and both histological and immunohistochemical analyses have defined the specific cell populations involved. In our experience, most leucocytes in these areas are monocyte-macrophages and their number is further enhanced when considering peri-glomerular granulomas.

Macrophages are generally believed to have a key role in progression of renal damage, and their participation to crescent formation has been demonstrated since 1976.
Some years ago we studied by immunohistochemistry and \textit{in situ} hybridization 25 renal biopsies of patients with ANCA-positive renal vasculitis, using various markers of macrophage adhesion, activation, proliferation and apoptosis.\textsuperscript{23} According to our findings, glomerular infiltration seems to involve two Ig-like adhesion molecules, intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1. Given its pattern of positivity, that exactly corresponds to the necrotizing-extracapillary area, and its \textit{de novo} synthesis in affected glomeruli, VCAM-1 appears

\textbf{Fig. 11.1} (a) and (b) Features of vasculitis, with necrosis of the vessel wall and leucocyte infiltration (PAS, Trichrome, 400×, 250×). (c) Isolated necrosis of the glomerular tuft (Trichrome, 600×). (d) A glomerulus displays a focal crescent accompanying the necrotic lesion (Trichrome, 250×). (e) Massive positivity of the 27E10 antigen is present in a granulomatous lesion (Immunoperoxidase, 250×). (f) Contemporaneous presence of active and sclerotic areas characterize this glomerulus (Trichrome, 250×).
especially relevant to this infiltrating process. This result, also observed by our group in other forms of glomerular capillaritis, for example necrotizing IgA nephritis, Henoch–Schönlein syndrome and glomerulonephritis associated with endocarditis, seems to consolidate the hypothesis that necrosis of glomerular capillaries and VCAM-1 production are strictly associated events. We can also suggest that in these lesions adhesion of macrophages might be prevalently VCAM-1-mediated, as supported by the strong positivity in the same areas of the VCAM-1 receptor VLA-4.

Another interesting observation coming from our investigation was related to the features of acute activation of macrophages involved in glomerular and interstitial granulomatous lesions, as demonstrated by the massive expression in these areas of the myeloid-related protein complex MRP8/14 (27E10 antigen, Fig. 11.1e). This means that acute granulomatous lesions of renal vasculitis are very different from other kinds of chronic tissue granulomas, in which MRP8/14 has been found completely negative.

Our work also confirmed previous findings of tumour necrosis factor (TNF-\(\alpha\)) expression in renal biopsies of ANCA-associated vasculitis, that was present in the same areas of macrophage accumulation. In recent years, patients with ANCA-associated vasculitis have been treated by inhibition of TNF-\(\alpha\) by etanercept (that mimics soluble TNF-\(\alpha\) receptors) or infliximab (anti-TNF-\(\alpha\) antibody), but the results have been conflicting and their safety and adverse effect profile remain unclear.

The last few decades have seen major changes in the management of ANCA-associated renal vasculitis. Nevertheless, current treatments are associated with substantial toxicity, with many patients experiencing repeated relapses and increased incidence of malignancy, infection and bone marrow suppression.

The pathological consequence of inadequate or ineffective therapy is the appearance of glomerular sclerosing lesions, most likely representing the end of a reparative phase of necrotizing crescentic damage and very common in repeat biopsies. The contemporaneous presence of necrotic and sclerotic lesions can also be observed, not only involving different glomeruli, but also appearing in the same glomerulus (Fig. 11.1f). Apart from repeat biopsies, focal and segmental glomerulosclerosis is found at the first renal biopsy in about 10–20% of cases. By light microscopy the lesion is quite specific, appearing as a well-delineated rounded area, that frequently adheres focally to the Bowman’s capsule through a small fibrous crescent. In cases where sclerosing lesions are prevailing, arteries also can disclose a segmental reparative pattern, with lumen narrowing and evident scarring lesions of the vessel wall. Monocyte-macrophages are likely also to have a role in this reparative processes, given their ability to produce substances directly involved in matrix remodelling, such as transforming growth factor (TGF)-\(\beta\). A positivity for TGF-\(\beta\) was in fact detected in necrotizing crescentic lesions by Yamamoto et al. and more recently by Gionanlis et al.

Apart from focal peri-glomerular infiltrates and interstitial granulomas, the examination of renal biopsies in ANCA-associated renal vasculitis discloses the almost constant presence of an intense, and diffuse interstitial infiltration, composed by equal numbers of T lymphocytes and macrophages, whereas granulocytes and B lymphocytes constitute a minor component. It is worth remarking, given the pauci-immune nature of the injury, that a scarce B lymphocyte participation induces a cell-mediated immunological mechanism to be predominant in renal vasculitis.
By definition, all these forms are termed ‘pauci-immune’, meaning that immunofluorescence can range from completely negative to weakly positive. However, in recent years a role for complement has been better defined and supported by experimental models and observations on human renal tissue.33

Besides complement components, in glomerular areas of necrotizing extracapillary lesions and in vessels affected by necrosis, fibrinogen always stains quite strongly.

By electron microscopy, electron-dense deposits parallel immunofluorescence findings, ranging from absent to scarce or more consistent presence, although generally showing irregular distribution.

The ultrastructural analysis can also be helpful in displaying glomerular endothelial damage, with segmental swelling and detachment from the basement membrane, presence of gaps in the glomerular basement membrane and ruptures of the Bowman’s capsule.

Take home points

1. ANCA-associated renal vasculitis, namely Wegener’s granulomatosis, MPA, renal limited vasculitis and Churg–Strauss syndrome, display the same pathological features at renal biopsy. Only true interstitial granulomas are diagnostic of Wegener’s granulomatosis.

2. Renal biopsy is a fundamental tool for diagnosis and management.

3. Glomerular and interstitial granulomas are acute lesions, very different from other kinds of chronic granulomatous reactions.

4. Despite the pauci-immune nature of the disease, a role for complement is emerging from more recent experimental and human studies.

5. Treatment options have largely improved prognosis, but relapses and adverse effects remain frequent and better therapies are still required.

References

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest

** Accurate and informative pathological description of different forms of RPGN.

** Clinical and pathological features of ANCA-associated renal vasculitis, described starting from clinical cases.

* One of the few published reviews on Churg–Strauss syndrome.

REFERENCES

   ** A recent practical guide to diagnosis of vasculitis.
   ** Practical guidelines towards Churg–Strauss syndrome diagnosis.
   ** A model of rapidly progressive GN highlighting the importance of HIF-1α and Cxcr4.
   ** A novel view of crescent formation from parietal renal progenitor cells.

*** The first manuscript focusing on the importance of macrophages in RPGN glomerular lesions.


* Research on human biopsies showing different types of macrophage activation in diseases with severe glomerular macrophage infiltration.


*** A review that summarizes new therapeutic approaches for treatment of ANCA-positive vasculitis.


*** A very accurate review on the role of complement in autoimmunity.
Chapter 12

Assessment of disease activity and damage in the ANCA-associated systemic vasculitides

Joanna C. Robson, Ravi Suppiah, and Raashid A. Luqmani

Introduction

In anti-neutrophil cytoplasm antibodies (ANCA)-associated vasculitis there are no universally applicable serological markers to assess disease activity or determine chronic sequelae. Inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are not specific to vasculitis but are useful as an adjunct when determining disease activity. Rising ANCA titres using highly sensitive new capture and anchor enzyme-linked immunosorbent assay (ELISA) methods may be of future clinical relevance in predicting relapse, but this technology is still in its infancy and cannot yet be recommended in this setting. Imaging modalities that can guide disease activity in large vessel vasculitis such as positron emission tomography (PET) scanning and magnetic resonance angiography (MRA) are not useful in small vessel vasculitis. Instead, our current method of determining disease activity and measuring chronic damage is to use specific clinical tools that have been developed and validated for this purpose. The main role of these instruments is to help guide or justify treatment decisions, serve as outcome measures for clinical trials and record the natural history of disease. We review the concepts of disease activity and disease damage, and provide an overview of the main clinical tools available for each function.

Disease activity

The European League Against Rheumatism (EULAR) recommend the use of the Birmingham Vasculitis Activity Score (BVAS) to standardize the assessment of disease activity in clinical trials involving the systemic vasculitides. The BVAS has largely superseded the use of other scales of activity such as the Groningen Index, the Disease Extent Index (DEI) and the Vasculitis Activity Index (VAI), which are described in Table 12.1, but are not discussed further in this chapter.
Table 12.1 Summary of vasculitis assessment tools

<table>
<thead>
<tr>
<th>Assessment tool</th>
<th>Description</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity tools</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Groningen Index</td>
<td>Scored on clinical signs and histology</td>
<td>Impractical for serial assessment because inclusion of histology, developed in GPA</td>
<td>Kallenberg et al.³</td>
</tr>
<tr>
<td>VAS</td>
<td>Nine rating scales for separate organ system involvement (graded 0–4) combined with laboratory tests</td>
<td>Easy to complete but subjective assessment involved in rating scales</td>
<td>Whiting-O’Keefe et al.⁵</td>
</tr>
<tr>
<td>Disease Extent Index</td>
<td>Signs and symptoms, and diagnostic procedures to be performed to confirm active vasculitis in 10 organ systems (each scoring 2) plus constitutional symptoms (scores 1)</td>
<td>Assessment of current damage and activity, designed for use in GPA. Weighting used</td>
<td>De Groot et al.⁴</td>
</tr>
<tr>
<td>Birmingham Vasculitis</td>
<td>Nine organ-based systems. Weighted to each individual item and maximum totals applied to each system</td>
<td>Physician must decide if items due to active vasculitis, BVAS2 column for persistent disease</td>
<td>Luqmani et al.⁶,⁷</td>
</tr>
<tr>
<td>BVAS (v. 3)</td>
<td>66 clinical features grouped into nine organ systems. Weighting according to perceived clinical relevance. Inclusion of some items requiring specialist opinion or further tests</td>
<td>Physician must decide if items due to active vasculitis, persistent disease now indicated by separate box if all items due to ongoing activity</td>
<td>Mukhtyar et al.¹³</td>
</tr>
<tr>
<td>BVAS/WG</td>
<td>Addition of ‘other section’ to nine organ systems used in BVAS. 34 separate disease items, chosen as more specific for GPA, further classified into major (organ- or life- threatening) or minor items</td>
<td>Only clinically validated for use in GPA, although shown to correlate to BVAS for other vasculitides when tested on paper cases</td>
<td>Stone et al.¹⁵</td>
</tr>
</tbody>
</table>
Table 12.1 (continued) Summary of vasculitis assessment tools

<table>
<thead>
<tr>
<th>Assessment tool</th>
<th>Description</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Damage assessment tools</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic Necrotizing Vasculitis (SNV) Damage Index</td>
<td>34 items. Scoring occurs if damage present for ≥6 months except for irreversible items such as stroke and myocardial infarction which are scored immediately. Some items have double weighting. Does not include items of damage in the ENT system</td>
<td>Superseded by VDI</td>
<td>Abu-Shakra et al. 17</td>
</tr>
<tr>
<td>Vasculitis Damage Index (VDI)</td>
<td>Generic tool for all types of vasculitis. 64 items grouped into 11 organ systems. No weighting of items in current version</td>
<td>One-page tool, easy to use. Validated and widely used</td>
<td>Exley et al. 19</td>
</tr>
<tr>
<td>ANCA Vasculitis Index of Damage (AVID)</td>
<td>Specific for ANCA-associated vasculitis. Left and right sides scored separately for damage to eyes and ears</td>
<td>Undergoing validation</td>
<td>Seo et al. 23</td>
</tr>
<tr>
<td>Combined Damage Assessment Index (CDA)</td>
<td>Specific for ANCA-associated vasculitis. 135 items in 17 organ systems. Left and right sides scored separately for damage to eyes and ears. Weighting of items is planned for the future</td>
<td>Undergoing validation</td>
<td>Seo et al. 23</td>
</tr>
<tr>
<td><strong>Prognostic tools</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Five-factor score (FFS)</td>
<td>Prognostic factors in PAN and CSS. The five factors are: renal failure, proteinuria, cardiomyopathy, GI tract involvement and CNS signs</td>
<td>FFS=0, 5-year mortality 11.9%; FFS=1, 5-year mortality 25.9%; FFS&gt;2, 5-year mortality 45.95%</td>
<td>Guillevin et al. 18</td>
</tr>
<tr>
<td>Vasculitis Damage Index (VDI)</td>
<td>Several studies have shown that the VDI score at different time points can be an important prognostic marker for future death and morbidity</td>
<td>A VDI score ≥5 at the 6-month time point has a HR of 12 for death at 2 years compared with those with a lower score</td>
<td>Exley et al. 19</td>
</tr>
</tbody>
</table>

(Continued)
BVAS was first published in 1994 and formalized the assessment of active vasculitis in nine specific organ systems: systemic; cutaneous; mucous membranes/eyes; ear, nose and throat; chest; cardiovascular; abdominal; renal and neurological. Symptoms and signs of organ involvement were recorded only if they could be attributed to vasculitis and not another cause such as infection or side effects from medications, and were designed to be easy to determine through history or examination. A few simple investigations such as urinalysis and serum creatinine were also included. Repeat biopsies that had been required in the previous Groningen Index of activity in patients with granulomatosis with polyangiitis (Wegener’s) were excluded on ethical and practical grounds. We tested the BVAS by studying 213 consecutive patients with different types of vasculitis and found the score feasible to use and that it had content validity (comprehensiveness) and face validity (credibility) when trialled by a group of physicians with an interest in vasculitis. The BVAS also made biological sense (construct validity) when measured against other scores of disease activity and was sensitive to change when measured serially in 30 patients who had episodes of both disease activity and inactivity during the study period. The BVAS score was weighted towards items representing objective evidence of organ involvement, (e.g. 10% rise in creatinine) as opposed to more subjective symptoms (e.g. malaise or arthralgia).

The design of the BVAS evolved through its use by the European Union Study Group of Therapeutic Trials in Systemic Vasculitis (ECSYSVASTRIAL) in clinical studies. Minor adjustments were made to the items included and for the first time the
presence of ‘smouldering’ disease, that is not new or worse but grumbling activity was recorded in a separate column (BVAS2), as were the results of specialist opinions from ear, nose and throat (ENT), cardiology or ophthalmologists. The BVAS has been used in more than 10 clinical trials to assess disease activity and define remission and relapse. The latest version of BVAS called the BVAS (v. 3) has further optimized the items included, excluding items with low specificity for vasculitis and grouping those due to the same pathological processes under the same headings. The previously used second column to record ongoing active features (BVAS2 column) has been exchanged for a single box for ‘persistent only disease’ to simplify the scoring system. Initial variation in scores between different physicians highlighted the need for adequate training to ensure that only items due to active vasculitis (rather than from infection or previous damage) are scored. The BVAS (v. 3) forms, training manual and glossary sheet are available online at the EUVAS website (http://www.vasculitis.org). The BVAS (v. 3) has been validated for assessment of activity of patients with systemic vasculitis, is reproducible and sensitive to change and demonstrates convergence with CRP, physician global assessment and treatment decisions. The BVAS has also been adapted for use in trials involving only patients with granulomatosis with polyangiitis (BVAS/WG) by concentrating on clinical features specific for patients with granulomatosis with polyangiitis (e.g. subglottic involvement) and excluding less relevant items (e.g. bruits or loss of pulses). The BVAS/WG index has been validated in simulation exercises and actual patients, is sensitive to change with good inter and intraobserver reliability and correlates with the physician’s global assessment. An exercise applying different assessment tools to paper cases with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis, found a high correlation in scores between the BVAS/WG, BVAS, physician’s global assessment and the DEI. The BVAS/WG should, however, still be used with caution in non-GPA vasculitis patients as it is yet to be clinically validated in this group.

**Disease damage**

The principle of disease damage in vasculitis is to measure chronic scarring that has resulted from vasculitis or its treatment. By definition, damage can only occur after the onset of vasculitis and represents permanent effects, even though the actual problem may be considered to have resolved (e.g. a myocardial infarction, from which the patient has made an apparent full recovery still represents permanent scarring in the myocardium). One of the important concepts of damage is to recognize components of disease that will not respond to further immunosuppressive treatment and therefore prevent inappropriate use of potentially harmful therapy. The concept is intuitive, but for accuracy, reproducibility and to monitor change over time there needs to be an easy and well-defined method of measuring damage. The VDI is the most widely used and validated method but a new tool called the Combined Damage Assessment index (CDA) is in the process of development and may have a role in clinical trials for ANCA-associated vasculitis. The benefits and drawbacks of these two damage tools are discussed below. An older damage tool called the Systemic Necrotizing Vasculitis (SNV) Damage Index is summarized in Table 12.1, but it is no longer used and therefore
not discussed further. The other tool that is sometimes considered in this category is the five-factor score (FFS), which was proposed by the French Vasculitis Study Group, but this is a prognostic score rather than a detailed damage assessment.

**VDI**

The VDI is a generic tool created by the Birmingham Vasculitis Group (UK) in 1997 and is designed to be used with all types of systemic vasculitis. The principles guiding damage assessment, the items included and the glossary of terms for the VDI were developed by consensus of experts in vasculitis. The VDI comprises 64 items grouped into 11 organ systems. An arbitrary time limit of ≥3 months is used as the cutoff for scoring an item of damage. For consistency, items such as stroke or myocardial infarction, which are discrete events, are still only scored after 3 months from the initial episode. Each item is scored as present or absent irrespective of the underlying cause as long as it has occurred after the onset of vasculitis. The intention is to capture damage due to disease or treatment but it is possible that other variables such as increasing age contribute to an increasing VDI score over time. There is no weighting of items; each item scored as present counts towards the total score (maximum possible = 64). Several groups have shown that the VDI score is an important prognostic marker. A score ≥1 on the VDI at time of first starting immunosuppression is a predictor of higher mortality (HR 6.1; 95% CI 1.7–22.1) in GPA. A score of ≥5 at 6 months in a cohort of mixed primary and secondary vasculitis showed a much higher risk of mortality by 2 years (HR 12.3; 95% CI 4.2–36.9). Studies using the VDI have also shown that the greatest accumulation of damage occurs in the first 6 months following a diagnosis of vasculitis. The VDI has been used as an outcome measure in most of the major clinical trials in ANCA-associated vasculitis over the past decade.

**CDA**

In 2008, an international group of investigators interested in outcome measures in vasculitis met in order to re-evaluate disease-specific damage assessment tools. At the time, the main clinical trials were in ANCA-associated vasculitis, and several years of use of the VDI in clinical trials had highlighted that it may not capture all damage attributable to this group of disorders. A group from North America had started developing a tool called the ANCA-associated Vasculitis Instrument of Damage (AVID), which is currently being assessed against the VDI in the RAVE (Rituximab for ANCA associated Vasculitis) Trial but results are not yet published. At the same time, investigators in Europe were attempting to revise the VDI to be more specific for ANCA-associated vasculitis. Considerable overlap was noted between the two separate efforts and therefore the group decided to merge both projects to create a new tool with input from experts from both sides of the Atlantic. To reflect this combined effort, the new tool was named the CDA.

The CDA comprises 135 items grouped into 17 categories, includes laterality for damage to the eyes and ears and records gradation of severity for eight items. The extra components (e.g. striae, easy bruising and weight gain) on the CDA (compared with the
VDI) are derived from information that was recorded in the ‘other’ category on the VDI for patients enrolled in the WGET trial (a randomized controlled trial comparing etanercept to placebo as adjunctive therapy in 180 patients with GPA) and distinguishes between left and right for damage to the eyes and ears. A weighting system is being developed for the CDA. A survey of 50 experts in vasculitis covering all relevant specialties has shown that malignancy, renal failure, severe respiratory compromise, cardiovascular disease and blindness should have the greatest importance, whereas items such as muscle atrophy, bruising, mouth ulcers, striae and alopecia should have the lowest. The other differences between the CDA and the VDI are that the time cutoff for damage is defined as ≥6 months and the item of damage must be attributable to vasculitis or its treatment. Recently, the CDA was compared with the VDI in a cross-sectional study of 285 patients with primary and secondary causes of vasculitis; the majority of patients (70%) had ANCA-associated vasculitis. Attribution to cause of damage was not applied and the ≥3 month time point was used for both the VDI and CDA. The findings were that the CDA was more sensitive at detecting damage but was more time-consuming and had lower inter- and intraobserver reliability than the VDI due to its complexity. The CDA is still a work in progress, and further work on a weighting system and evaluation in a longitudinal study are still required. It is likely to be most useful as an outcome measure for clinical trials.

Functional assessment

With improvement in immunosuppressive therapy for the treatment of systemic vasculitis, patients are now surviving for longer, but the effect of pain and other disease symptoms can result in significant impairments to quality of life. Self-reported assessment tools to measure quality of life such as the Short Form (SF)-36, and the Health Assessment Questionnaire (HAQ) to measure levels of physical functioning and disability are established tools for use in patients with chronic disease and have been used in patients with vasculitis. The OMERACT Vasculitis Working Group has recognised that developing vasculitis-specific patient reported outcome measures (PROMs) is an essential area for future research, because generic tools such as the SF-36 may not be precise enough to accurately measure change in this set of chronic complex multi-system diseases.

Conclusion

There is no gold standard for the assessment of disease activity and damage in patients with systemic vasculitis. The tools developed so far have been important in standardizing the approach to both individual patients and the assessment and treatment decisions in clinical trials. However, these tools are imperfect and need ongoing review and refinement. In the future, new biomarkers, or other surrogate markers may be incorporated into, or surpass these instruments. Issues such as which outcomes are important to physicians compared with what patients regard as important will need to be considered when assigning weight to specific components of disease activity and damage and, ideally, will involve a data-driven process.
**Take home points**

1. Currently there is no available gold standard method of assessment of disease activity; inflammatory markers can be non-specifically raised with infection or malignancy, rises in ANCA titre do not reliably predict clinical relapse and imaging modalities such as PET or MRI are not helpful in small vessel vasculitis.

2. In ANCA-associated vasculitis, disease activity and damage are both measured using specific validated clinical tools.

3. Disease activity is measured using the BVAS, which is a formalized assessment of active vasculitis over nine specific organ systems (systemic, cutaneous, mucous membranes/eyes, ENT, chest, cardiovascular, abdominal, renal and nervous systems).

4. Disease damage is measured using the VDI, which includes 64 items over 11 organ systems. Damage can be secondary to the effects of acute vasculitis or its treatment, with items only recorded if they have been present for more than 3 months.

5. Significant impairments in health-related quality of life have been demonstrated in patients with ANCA-associated vasculitis using generic tools such as the SF-36. The OMERACT vasculitis working group have identified the need to develop a vasculitis-specific patient reported outcome.

**References**

Papers of particular interest have been highlighted as:

* of special interest

** of outstanding interest


** Includes EULAR recommendations on the use of validated tools to measure disease activity and damage in clinical trials in systemic vasculitis.


   * Demonstration of impairment in health-related quality of life in patients with vasculitis.

   * Further evidence of impairment in health-related quality of life in patients with vasculitis.


   ** The OMERACT vasculitis working group details the use of established clinical tools to measure a range of outcomes and highlights areas where further research is needed.
Chapter 13

The clinical presentation and treatment of renal vasculitis

David Jayne

Summary

The kidney is the most commonly affected vital organ in anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis, and patient outcomes are dominated by the severity of renal disease at diagnosis and by its response to treatment. Without adequate therapy most patients will progress to end-stage renal disease (ESRD). The insidious nature of renal vasculitis is reflected by frequent delays in diagnosis unless extra-renal vasculitis, for example of the ear, nose and throat (ENT) system in Wegener’s granulomatosis, raises suspicion. Because urinary abnormalities are always present when renal vasculitis is active and because treatment can rescue long-term renal function, it is particularly important to have a high index of suspicion for this diagnosis in a wide variety of clinical settings. Evidence for the effectiveness of current treatment regimens is robust but drug toxicity remains a major problem and regimens and specialized observation need to be prolonged due to the risks of relapse and increased frequency of severe co-morbidities. International consensus treatment recommendations are now available.¹

Introduction

Classification

ANCA-associated vasculitis (AAV) occurs usually as a primary, autoimmune, disorder but occasionally, is secondary to another disease process, such as drug hypersensitivity, malignancy or chronic infection. The term arose from the association of ANCA with both Wegener’s granulomatosis and microscopic polyangiitis, from the similarities in renal histology when the kidney is affected by these disorders and by the assumption of a common pathogenetic pathway related to the immunological activity of ANCA themselves.² Up to 50% of patients with Churg–Strauss angiitis are also ANCA positive, and this subgroup has an increased frequency of renal involvement.³ Those presenting just with renal disease have also been termed ‘idiopathic rapidly progressive glomerulonephritis’ or ‘renal-limited vasculitis’, but can be regarded as a forme fruste of microscopic polyangiitis. ANCA are not detectable in 5% of microscopic polyangiitis cases with renal involvement and the absence of ANCA does not exclude this diagnosis. ANCA with antigenic specificity for proteinase 3 (PR3-ANCA) is present in the majority of Wegener’s granulomatosis patients but also in some with microscopic polyangiitis,
whereas myeloperoxidase ANCA (MPO-ANCA) predominates in microscopic polyangiitis, Churg–Strauss angiitis and drug-induced vasculitis (Table 13.1). There may be involvement of larger arteries in both Wegener’s granulomatosis and microscopic polyangiitis, raising the possibility of polyarteritis nodosa or a large vessel vasculitis, but if microscopic vasculitis is present, such as glomerular capillaritis, then ANCA is usually present and the diagnosis of an AAV is made.

**Pathology**

AAV causes a crescentic glomerulonephritis with focal glomerular necrosis. Glomerular immune deposits are scanty or absent, ‘pauci-immune’, but there is a neutrophil predominant infiltrate in and around the glomerulus with activated lymphocytes; occasional eosinophils may also be present. Although predominantly a glomerulonephritis, tubulo-interstitial inflammation and injury is often present and 15% have vasculitis of extra-glomerular vessels. Granulomata are rare, although a ‘pseudo-granulomatous’ reaction may be seen around the glomerulus. The glomerular histology of ANCA vasculitis has been subclassified according to renal prognosis into focal, crescentic, mixed and sclerotic subgroups (Table 13.2).  

**Table 13.1** Renal involvement in ANCA vasculitis syndrome

<table>
<thead>
<tr>
<th>ANCA vasculitis syndrome</th>
<th>Renal involvement (percentage)</th>
<th>ANCA subtype</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener’s granulomatosis</td>
<td>70%</td>
<td>PR3-ANCA (80%)</td>
<td>More frequent in older patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rarely. MPO-ANCA</td>
</tr>
<tr>
<td>Microscopic polyangiitis (renal limited vasculitis)</td>
<td>90% (100%)</td>
<td>MPO-ANCA (60%) or PR3-ANCA (35%)</td>
<td>5% ANCA negative</td>
</tr>
<tr>
<td>Churg–Strauss angiitis</td>
<td>15%</td>
<td>MPO-ANCA (50%)</td>
<td>Renal involvement more frequent if ANCA positive</td>
</tr>
<tr>
<td>Drug-induced vasculitis</td>
<td>75%</td>
<td>MPO-ANCA</td>
<td>Other ANCA specificities may also be present</td>
</tr>
</tbody>
</table>

ANCA, anti-neutrophil cytoplasm antibodies; MPO, myeloperoxidase; PR3, proteinase 3.

**Table 13.2** Classification of ANCA-associated renal vasculitis

<table>
<thead>
<tr>
<th>Class</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>&gt;50% normal glomeruli</td>
</tr>
<tr>
<td>Crescentic</td>
<td>&gt;50% glomeruli with cellular crescents</td>
</tr>
<tr>
<td>Mixed</td>
<td>&lt;50% normal, &gt;50% crescentic</td>
</tr>
<tr>
<td>Sclerotic</td>
<td>&gt;50% globally sclerotic glomeruli</td>
</tr>
</tbody>
</table>

Pauci-immune staining pattern on immunofluorescence microscopy and ≥1 glomerulus with necrotizing or crescentic glomerulonephritis on light microscopy are required for inclusion in all four classes.

ANCA, anti-neutrophil cytoplasm antibodies.
Extra-renal vasculitis

As a systemic disease, AAV typically commences with constitutional symptoms before focal disease, such as, rash, arthritis, lung or renal involvement becomes apparent. The presence of extra-renal disease influences the rapidity of diagnosis, treatment regimens and prognosis of patients with renal disease, and an awareness of the systemic nature of the disease is central to diagnosis and management.

Epidemiology

The incidence of AAV is 15–20/million/year with a prevalence of 90–400/million. Both Wegener’s granulomatosis and microscopic polyangiitis have an increased incidence with age, with the most common age at diagnosis for Wegener’s granulomatosis being 50–60 years, and microscopic polyangiitis over 65 years (Fig. 13.1). Thus, the frequency of ANCA-associated renal vasculitis also increases with age with the proportion of native kidney biopsies displaying a crescentic nephritis rising from 5% in those under 60 years to over 11% in those over 60 years of age, of which ANCA vasculitis is the most common diagnosis. Renal function at diagnosis is lower in older patients, indicating that not only is renal involvement more frequent but it is more aggressive. Silica exposure increases the incidence of microscopic polyangiitis and an association with farming, especially with animals, has also been demonstrated.5 The relative frequencies of Wegener’s granulomatosis and microscopic polyangiitis are influenced by latitude, with Wegener’s granulomatosis being more frequent in colder climates in both the North and South hemispheres.6 In addition, there are ethnic differences, with Wegener’s granulomatosis being less common in eastern Asian and black populations.

Clinical presentation

There is considerable variety in clinical presentation of ANCA-associated renal vasculitis, yet an imperative to aim for early diagnosis because delay increases the risks of ESRD

Fig. 13.1 The frequency of Wegener’s granulomatosis and microscopic polyangiitis according to patients’ age at diagnosis (data from three clinical trials performed by the European Vasculitis Study Group).
and early death. First, there should be suspicion of a vasculitic illness in certain clinical settings (Table 13.3); second, an investigative pathway should lead to confirmation of vasculitis or an alternative illness; third, the vasculitis diagnostic subgroup and extent and severity of the disease is determined.

**The prodromal phase**

Most patients will report several months of constitutional symptoms before a diagnosis of AAV is made. The average duration has shortened from over 1 year to under 6 months with increased awareness and use of the ANCA test. Constitutional symptoms comprise fevers, malaise, fatigue, weight loss, headache, polymyalgia and polyarthralgia. Focal signs of vasculitis may come and go, such as flitting arthritis, purpuric rash or skin ulceration, mouth ulceration and episcleritis. Alternative diagnoses including influenza, polymyalgia rheumatica or rheumatoid arthritis may be made and their treatment may delay and complicate the diagnosis.

**Extra-renal presentations**

The presence of a non-renal feature of vasculitis, in particular ENT disease, facilitates an earlier diagnosis of ANCA-associated renal vasculitis and improved outcomes (Table 13.3). However, the presentation of patients to different specialists with varying

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**Table 13.3** Clinical scenarios when ANCA-associated vasculitis should be suspected

<table>
<thead>
<tr>
<th>Constitutional symptoms</th>
<th>Flu-like symptoms, fever, malaise, headache, polymyalgia, polyarthralgia, weight loss lasting for more than 2 weeks without alternative explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal signs</td>
<td>Flitting arthritis, episcleritis, purpuric rash, skin ulceration or mononeuritis multiplex</td>
</tr>
<tr>
<td></td>
<td>Chronic ENT symptomatology such as, sinusitis, nasal polyps, epistaxis, nasal congestion, otitis media, hoarseness or stridor</td>
</tr>
<tr>
<td></td>
<td>Respiratory symptoms of dyspnoea, cough, haemoptysis, wheeze without alternative explanation</td>
</tr>
<tr>
<td></td>
<td>‘Antibiotic-resistant pneumonia’</td>
</tr>
<tr>
<td>Renal features</td>
<td>Microscopic or macroscopic haematuria with proteinuria</td>
</tr>
<tr>
<td></td>
<td>Deteriorating renal function with haematuria and proteinuria and normal sized kidneys</td>
</tr>
<tr>
<td></td>
<td>Unexplained chronic kidney disease with microscopic haematuria</td>
</tr>
<tr>
<td></td>
<td>(Rarely: nephrotic syndrome, ‘focal segmental glomerulosclerosis’, ureteric stenosis with hydronephrosis, renal rupture with peri-renal haematoma)</td>
</tr>
<tr>
<td>In the context of another disease, drug or occupation</td>
<td>Anti-glomerular basement membrane disease</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>Chronic lung disease including bronchiectasis and cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>Treatment with hydralazine, penicillamine or minocycline</td>
</tr>
<tr>
<td></td>
<td>Prolonged silica exposure</td>
</tr>
</tbody>
</table>

ANCA, anti-neutrophil cytoplasm antibodies; ENT, ear, nose and throat.
interest and experience with vasculitis complicates and delays the diagnosis. It is important that individual specialties develop thresholds for initiating a vasculitis work-up, especially when the presenting symptom, for example, chronic sinusitis, is common and the proportion due to vasculitis is very low. In Wegener’s granulomatosis, naso-sinus and ear disease usually, but not always, precedes renal disease and in Churg–Strauss angiitis there is typically a long prodrome of naso-sinus disease and worsening asthma. Renal involvement in microscopic polyangiitis is usually present at the time of diagnosis. Alveolar capillaritis presents with radiological infiltrates, dyspnoea, haemoptysis and a fall in haemoglobin, and accompanies 25% of cases of ANCA-associated renal vasculitis. It usually occurs at the same time and represents a similar pathogenetic insult. When severe it is termed the pulmonary renal syndrome, although ANCA vasculitis is not the only cause of this presentation.\textsuperscript{8}

Renal features

The insidious nature of renal disease contributes to late diagnoses particularly in those with renal-limited vasculitis who can present with advanced renal failure and symptoms of uraemia. Vasculitis should be suspected in any patient with haematuria and proteinuria. AAV is the most common cause of the syndrome of rapidly progressive glomerulonephritis: deteriorating renal function with a crescentic glomerulonephritis on renal biopsy. In an elderly patient, ANCA-associated renal vasculitis is the most common cause of acute renal failure with normal sized kidneys without an obvious precipitant. However, renal involvement is increasingly diagnosed with normal or near-normal serum creatinine due to the presence of other features of vasculitis or a positive ANCA. Less common presentations are slowly progressive renal disease with microscopic haematuria, and nephrotic syndrome, when a focal segmental glomerulonephritis can be seen on biopsy. Churg–Strauss angiitis can cause ureteric strictures and hydronephrosis, and larger renal arteries may be involved in microscopic polyangiitis leading to regional infarction as seen, classically, in polyarteritis nodosa.

Haematuria can be macroscopic with ‘smoky’ urine, and usually has at least 100 red cells per high powered field on microscopy when dysmorphic erythrocytes are seen. Red cell urinary casts are present in active renal vasculitis, other urinary casts have no significance. Blood pressure is not routinely elevated and a high blood pressure may indicate the presence of larger artery involvement. Rupture of the kidney with perirenal haematoma can occur as a consequence of severe renal inflammation. Proteinuria is present but is rarely in the nephrotic range, paradoxically, proteinuria rises after the onset of treatment reflecting glomerular damage and remodelling.

Renal ultrasound is unremarkable or shows mildly enlarged kidneys. Wedge-shaped infarction suggests an overlap with polyarteritis nodosa.

AAV with anti-glomerular basement membrane (GBM) disease: Some 5% of AAV patients present with simultaneous renal vasculitis and anti-GBM disease.\textsuperscript{9} They are older, have more severe renal disease and are more likely to have pulmonary involvement than other AAV cases. The serology demonstrates ANCA, usually MPO-ANCA, positivity and anti-GBM antibodies. Renal histology reveals an aggressive crescentic glomerulonephritis, typically involving all glomeruli with linear IgG deposition on immunofluorescence. When presenting in renal failure, such patients are more likely
to recover renal function than in pure anti-GBM disease. However, after the initial presentation, unlike in anti-GBM disease, they can follow a relapsing course with persisting ANCA positivity.

### Disease states

Patients with primary systemic vasculitis vary in the pattern and severity of organ involvement, in their response to therapy and in their subsequent disease course and prognosis. Diagnosis is preceded by a prodromal phase, clinical evaluation confirms the extent and severity of organ involvement, which permits the patient to be placed in a subgroup to guide therapy (Table 13.4). Appropriate treatment aims to obtain and sustain disease remission but relapses are common and refractory disease or chronic, persisting low disease activity states represent therapeutic challenges (Table 13.5).

### Investigations

#### Serology

Diagnosis depends on the triad of clinical features, serology and histology, and the exclusion of secondary causes. ANCA positivity confirmed by a positive PR3-ANCA or MPO-ANCA has a predictive value above 95% for the diagnosis of AAV with renal involvement in a patient with suspected nephritis. However, 5–10% of patients with a pauci-immune, necrotizing, crescentic glomerulonephritis are ANCA negative. ANCA positivity by indirect immunofluorescence (i.e. C-ANCA or P-ANCA) with negative PR3-ANCA and MPO-ANCA is still compatible with a diagnosis of AAV, but other chronic inflammatory processes that can produce a C-ANCA or P-ANCA need to be considered.
Renal biopsy

Renal biopsy enables a more secure diagnosis to be made. There is a debate as to the diagnostic value of renal biopsy when PR3-ANCA or MPO-ANCA are positive and the clinical presentation is typical. However, biopsy also permits diagnosis of concurrent conditions, such as anti-GBM disease or IgA nephropathy, and carries prognostic significance. Biopsy is strongly recommended when PR3-ANCA or MPO-ANCA are negative. Renal biopsy is unlikely to reveal a renal vasculitis in the absence of microscopic haematuria and proteinuria and is not indicated in a potential vasculitis patient purely on the basis of extra-renal disease.

The typical renal biopsy features in AAV are a pauci-immune necrotizing glomerulonephritis with crescent formation. Microscopic polyangiitis is associated with more severe biopsy changes with more evidence of chronicity and scarring. In Wegener’s granulomatosis acute tubular changes are more frequent, scarring is less apparent and the prognosis is better. For early presentations, the focal nature of the disease means that vasculitis cannot be excluded by a normal small biopsy, less than 10 glomeruli. Also, in an individual case, the predictive value of biopsy is not sufficiently robust to dictate therapy and the presence of severe scarring does not exclude the possibility of a good renal outcome.
There are no agreed diagnostic criteria for primary systemic vasculitis syndromes but there is consensus on diagnostic terminology and disease definitions. Diagnosis relies on clinical presentation supported by the results of ANCA testing and renal biopsy. For incomplete presentations a period of observation and assessment of treatment response will increase or reduce confidence in the diagnosis. Overlaps between vasculitic syndromes occur, for example an ANCA positive necrotizing glomerulonephritis in the context of giant cell arteritis.

**Differential diagnosis**

Secondary causes of vasculitis and diseases mimicking vasculitis need to be excluded before a diagnosis of primary systemic vasculitis can be made. Chronic inflammatory disorders, such as bacterial endocarditis or rheumatoid arthritis, can both mimic vasculitis, for example with constitutional symptoms and renal impairment, or induce a systemic vasculitis syndrome, for example an AAV. Chronic bacterial infection may be obvious, as in cystic fibrosis or bronchiectasis, but occult endocarditis or abdominal sepsis should be considered. Tuberculosis and other non-vasculitic causes of pulmonary cavities can mimic Wegener’s granulomatosis. Hepatitis C is the most common cause of cryoglobulinaemic vasculitis but has also been linked to other forms of vasculitis. For those presenting with deteriorating renal function, other causes of rapidly progressive renal failure; such as, myeloma kidney, atheroembolic renal disease, interstitial nephritis and acute tubular necrosis need to be considered. Reduced renal size points to more chronic causes of renal disease, such as hypertension or diabetes. The presence of microscopic haematuria and proteinuria is non-specific, occurring in other forms of renal and lower urinary tract inflammation and infection.

**Treatment**

**Aims of therapy**

Without therapy, renal vasculitis in the ANCA vasculitides will usually progress to ESRD. Current regimens aim to suppress manifestations of disease activity and achieve a ‘remission’ in order to avoid further vital organ damage, rescue renal function and reduce constitutional disturbance. Following diagnosis and assessment of the extent and severity of disease, the treatment induction phase, of 3–6 months, aims to control active features of vasculitis. Therapy is continued during the maintenance or remission phase, of 2 to at least 4 years, to consolidate disease control and prevent relapse. Over the longer term, attention is focussed at managing the consequences of vasculitic injury, such as chronic kidney disease, the effects of cumulative drug exposure, and the increased risks of cardiovascular disease and malignancy (Fig. 13.2).

**Induction therapy**

The combination of cyclophosphamide and high-dose corticosteroids, introduced over 30 years ago, remains the ‘standard of care’ for renal vasculitis. Cyclophosphamide is equally effective as a daily oral, or pulsed intravenous preparation (Table 13.6). However, the pulsed protocols expose the patient to a lower cumulative cyclophosphamide
Leukopenia is more common with daily oral cyclophosphamide and is an important risk factor for severe infection. Cyclophosphamide is continued for 3–6 months, by which time vasculitis will have been controlled in 90%. Improvement in renal vasculitis is mainly judged by improvement or stability of renal function and control of extra-renal vasculitis and the C-reactive protein (CRP). Microscopic haematuria persists for many months after the onset of therapy and proteinuria typically increases during the recovery period, occasionally to levels sufficient to cause the nephrotic syndrome. ANCA levels are not used to guide the duration or intensity of induction therapy. The elimination of cyclophosphamide and its active metabolites is influenced by age and renal function and doses should be reduced accordingly.

* Fig. 13.2 Flow chart of treatment phases and interventions for ANCA-associated renal vasculitis. GFR, glomerular filtration rate.

Dose and permit bladder protection through re-hydration and the use of Mesna. Leukopenia is more common with daily oral cyclophosphamide and is an important risk factor for severe infection. Cyclophosphamide is continued for 3–6 months, by which time vasculitis will have been controlled in 90%. Improvement in renal vasculitis is mainly judged by improvement or stability of renal function and control of extra-renal vasculitis and the C-reactive protein (CRP). Microscopic haematuria persists for many months after the onset of therapy and proteinuria typically increases during the recovery period, occasionally to levels sufficient to cause the nephrotic syndrome. ANCA levels are not used to guide the duration or intensity of induction therapy. The elimination of cyclophosphamide and its active metabolites is influenced by age and renal function and doses should be reduced accordingly.

** Close monitoring of the full blood count is required for the early detection of cytopaenias and appropriate dose adjustment. Prednisolone is commenced at high dose, 1 mg/kg/day, and reduced in steps to 5–10 mg/day
Additional treatment with intravenous methyl prednisolone, 1000–3000 mg, is widely used for renal vasculitis without a firm evidence base, and may be commenced on suspicion of the diagnosis before ANCA testing or renal histology is available. Plasma exchange improves the chances of renal recovery in those presenting in renal failure, creatinine >500 μmol, but it is uncertain whether it also has a role in renal vasculitis with deteriorating renal function below this level, or in severe non-renal presentations, such as, diffuse alveolar haemorrhage.

The increasing evidence for the pathogenicity of ANCA in renal vasculitis provides a rationale for its use, but removal of coagulation factors, cytokines or other substances may also be important. Plasma filtration or centrifugation appear equally effective and, on average, seven daily or alternate day exchanges of 1–1.5 plasma volumes are used. The procedure usually requires central vascular access, and may be complicated by haemorrhage and thrombocytopenia.

B cell depletion with rituximab has recently been shown, in two randomized trials, to be as effective as cyclophosphamide for the control of renal vasculitis. The RITUXVAS trial employed two cyclophosphamide pulses with rituximab but the results in the RAVE trial, when no cyclophosphamide was used, were similar. No early benefits of cyclophosphamide avoidance were observed in either trial. The longer-term effects of rituximab, as opposed to cyclophosphamide induction, are not known, especially the relapse risk and need for remission maintenance therapy. Rituximab can be recommended for remission induction when cyclophosphamide is contraindicated, for example, by infection, cytopenia, intolerance or strong desire to avoid its use.

Table 13.6 Cyclophosphamide dosing in the European Vasculitis Study Group, ‘CYCLOPS’ trial

<table>
<thead>
<tr>
<th>Pulsed cyclophosphamide dosing (mg/kg/pulse) with reductions for impaired renal function and age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>&lt;60</td>
</tr>
<tr>
<td>60–70</td>
</tr>
<tr>
<td>&gt;70</td>
</tr>
</tbody>
</table>

Timing of cyclophosphamide pulses

Weeks: 0, 2 and 4, then every 3 weeks (weeks 7, 10, 13, 16, 19, 21 and 24)*

Daily oral cyclophosphamide dosing

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Dose (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>2.0</td>
</tr>
<tr>
<td>60–70</td>
<td>1.5</td>
</tr>
<tr>
<td>&gt;75</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Current recommendations suggest duration of cyclophosphamide is a minimum of 3 and maximum of 6 months. See www.vasculitis.org for further details.
The alternative immunosuppressives, methotrexate, azathioprine and mycophenolate mofetil have been used in milder cases as induction agents in place of cyclophosphamide. The evidence is strongest for methotrexate in patients with non-renal vasculitis or renal vasculitis with normal renal function, but subsequent relapse rates were higher than with cyclophosphamide.

Treatment intolerance or severe infection are the most common causes of treatment failure in the induction phase. Progressive disease is treated first with intravenous methyl prednisolone and/or plasma exchange. If this fails or there is treatment intolerance, or active disease persists beyond 6 months, then agents used for refractory vasculitis are employed (see below).

**Maintenance therapy**

Disease relapse occurs in 75% of Wegener’s granulomatosis and 50% of microscopic polyangiitis cases by 5 years. The goals of the maintenance therapy are to prevent disease relapse with less risk of drug toxicity than during the induction phase. Cyclophosphamide is withdrawn and substituted by azathioprine or methotrexate, which are equally effective for remission maintenance. Azathioprine allergy or intolerance occurs in 5–10% and testing for thiopurine s-methyltransferase (TPMT) activity identifies rare patients at risk of severe myelosuppression. Hypersensitivity reactions can be difficult to distinguish from infection or vasculitic relapse, but their onset within 2–3 weeks of commencing azathioprine is an indicator. Methotrexate is excreted by the kidneys and should be avoided in the presence of renal impairment, glomerular filtration rate <50 ml/min. Although rare, concerns over methotrexate pneumonitis complicate its use in the presence of pulmonary vasculitis. Leflunomide has been shown to be superior to methotrexate for the prevention of relapse in Wegener’s granulomatosis and mycophenolate mofetil was less effective than azathioprine for the prevention of relapse in AAV after cyclophosphamide induction therapy. Prednisolone is either continued in conjunction with an immunosuppressive or is withdrawn at the end of the induction phase. There is an increased relapse risk following steroid withdrawal, which has to be balanced against the toxicity of long-term administration. Treatment withdrawal is the strongest relapse predictor, other predictors are a diagnosis of Wegener’s granulomatosis, persisting or return of ANCA positivity, a previous history of relapse and ENT involvement. ANCA levels are not closely related to disease activity, but the persistence of ANCA at 6 months after induction therapy, or a rising ANCA level indicate that relapse is more likely. This is particularly useful when treatment is withdrawn, relapse being almost inevitable if ANCA remains positive. There should be consideration for very prolonged low-dose immunosuppression in these cases.

Vasculitis relapse is classified as minor or major depending on the threat to vital organ function. The severity and consequences of relapse are dependent on how quickly relapse is detected. Renal relapse is initially manifested by a return or increase in haematuria with proteinuria with subsequent deterioration in renal function and is usually, but not always, associated with ANCA positivity and rises in erythrocyte sedimentation rate (ESR) and CRP. Repeat renal biopsy is indicated if there is uncertainty as to whether or not renal relapse is occurring. Such relapses are treated by a return to an induction protocol with cyclophosphamide or rituximab. In this subgroup, the
RAVE trial found rituximab more effective, in part due to the lower tolerability of repeated cyclophosphamide courses.

Response to therapy and resistant renal vasculitis

When renal vasculitis has caused renal impairment, a response to therapy is indicated by an improvement in serum creatinine, usually within the first 2 weeks. Renal function then continues to improve for 6–12 months. Haematuria is slower to respond but should fall below 100 red cells per high powered field by 3 months and continue falling thereafter. Proteinuria may rise early in the recovery phase and then persists for longer than haematuria, but full recovery is accompanied by resolution of haematuria to less than five red cells per high powered field and proteinuria below 0.5 g/24 hours. A failure of an elevated serum creatinine to fall or persistent high levels of haematuria indicate resistant renal vasculitis. Relative cyclophosphamide underdosing is indicated by a failure to induce lymphopaenia and is more common with intermittent pulsed administration. A failure to induce B cell depletion indicates that rituximab will be ineffective. Where there is uncertainty as to whether renal vasculitis remains active, a repeat renal biopsy can be performed after 4–6 weeks.

For patients dialysis-dependent at presentation, if recovery occurs it is usually seen within 2–3 weeks although, rarely, later renal recovery occurs. If no recovery has been seen after a course of plasma exchange has been completed, a persisting high ANCA level, high CRP attributed to vasculitis or poor control of extra-renal vasculitis suggest that renal vasculitis is likely to be still active and further plasma exchange would be beneficial. However, if there is no recovery by 4–6 weeks, further intensive therapy is likely to be unproductive.

Management of refractory disease

Refractory vasculitis occurs in 10–20% during the induction phase and is more common later in the disease course in non-renal Wegener’s granulomatosis. The re-introduction of conventional agents including intravenous methyl prednisolone, plasma exchange and cyclophosphamide can control most acute cases of refractory disease. However, their use may be complicated by intolerance, intercurrent infection or concern over a high cumulative exposure to cyclophosphamide.

Rituximab is effective in refractory vasculitis, and appears safe and is probably the drug of choice in this setting.33+ Immunosuppressives are withdrawn after rituximab and re-treatment at the time of ANCA rise or subsequent relapse is effective. The therapeutic effect of rituximab may be delayed by 2–3 months, during which time increases in prednisolone or cyclophosphamide may be required.

High-dose intravenous immunoglobulin reduces levels of vasculitic activity in persisting or relapsing vasculitis, reduces ANCA production and is a useful short-term additional agent permitting reduction in immunosuppressive or steroid dosing.34 This is desirable in the face of active infection, in patients at high risk of infection, such as, on the intensive care unit; and in pregnancy. Blockade of tumour necrosis factor-α with infliximab or etanercept has led to remission when used also as an additional agent, but prolonged use appears ineffective and it may increase the risk of infection.35+ T cell depletion with anti-thymocyte globulin or alemtuzumab (CAMPATH 1-H) has led to
remissions in refractory disease but carries a high risk of infective mortality in those over 60 years or those with uraemia.  

**ESRD and transplantation**

In renal-limited vasculitis, treatment with immunosuppression and prednisolone can be withdrawn once ESRD is established. However, in Wegener’s granulomatosis and microscopic polyangiitis continued therapy is required to control extra-renal vasculitic disease. Relapse rates of AAV are lower in patients with ESRD but relapse, especially of the respiratory tract, may still occur. ESRD vasculitis patients have a higher incidence of infection, which complicates therapy. The success of renal transplantation in AAV is similar to that for other non-diabetic causes of ESRD. Transplantation reduces the risk of vasculitic relapse and can proceed in the face of a persistently positive ANCA; however, ANCA positivity has been linked to vasculopathy in the allograft but not reduced survival. Previous cyclophosphamide and corticosteroid exposure places vasculitis patients at increased risk of opportunistic infection after transplantation. Recurrent vasculitis in renal allograft occurs in 1–3% and is treated with cyclophosphamide or rituximab.

**Adverse events of therapy**

The major early risk of combined cyclophosphamide and glucocorticoid treatment is sepsis, often associated with leukopaenia, which increases the septic risk more than fourfold. A causal sequence of cyclophosphamide-induced neutropaenia, sepsis and death, has been established and cyclophosphamide dosing should aim to minimize the risk of neutropaenia. Older age and uraemia greatly increase the risk of sepsis, in part due to the increased myelosuppressive effects of cyclophosphamide; impaired neutrophil function may also contribute to susceptibility to infection.

Thrombo-embolic events, including pulmonary emboli, and myocardial infarction and stroke occur in 7–15% during the first year. Glucocorticoid-related side-effects are very frequent and include fluid retention, weight gain, hypertension, diabetes and steroid-induced bone disease. The treatment of elderly patients with severe renal disease is a particular challenge due to their high risks of infection and treatment intolerance and lower glucocorticoid doses have been recommended.

**Prognosis and outcome**

Early mortality predictors are older age, infection or leukopaenia, within the first 3 months of therapy, a low glomerular filtration rate (GFR) and cumulative cyclophosphamide exposure. Later predictors include MPO-ANCA, and response to therapy. Those presenting in renal failure have a particularly poor outcome and earlier diagnosis is likely to improve outcome more than improved therapies. Mortality of AAV at 1 and 5 years is 10 and 40% respectively. For those under 60 it is 5% at 1 year; this rises to 23% for those over 60 and 44% for those over 70 (Fig. 13.3). In part, this is due to more advanced renal disease with more chronicity on renal biopsy in the elderly but intolerance of therapy and infections are major contributors. If treatment of renal vasculitis is unsuccessful and the patient progresses to ESRD, mortality is particularly high, over 50% after 1 year. Dual positive presentations of anti-GBM disease and vasculitis...
are associated with aggressive pulmonary and renal disease and poor outcomes. Specific renal predictors of ESRD include a lack of response to therapy, a high level of proteinuria during the recovery phase failure, the proportion of fibrotic crescents, extra-glomerular arteritis or arteriosclerosis and tubulo-interstitial scarring. A high proportion of normal glomeruli, glomeruli with active crescents and acute tubular necrosis in the renal biopsy are predictors of a good renal outcome. The overall disease activity at diagnosis, as measured by the Birmingham Vasculitis Activity Score, is predictive of the burden of irreversible damage the patient acquires and their mortality risk.

For those presenting with renal impairment who respond to therapy, there is a gradual improvement in renal function over the first year. GFR may then remain stable for many years even if recovery is to a GFR below 30 ml/minute. In this setting, vasculitis relapse with renal involvement carries a high risk of ESRD. A small group of patients develop progressive glomerulosclerosis and lose renal function without reactivation of vasculitis. Blockade of the renin–angiotensin system may improve renal outcome but requires further study.

Cardiovascular events are common during periods of active vasculitis and may be caused by the increased pro-thrombotic tendency. There is also an increased cardiovascular risk during follow-up that is higher than that seen in other patients with chronic kidney disease and may relate to more widespread vascular injury at the time of active vasculitis or the consequences of chronic renal failure and long-term medication. Malignancy rates at 5 years are 10–15%, which is an increase on expected rates. A wide distribution of malignancies is seen, with bladder malignancies over-represented reflecting cyclophosphamide exposure. One study found a cyclophosphamide threshold exposure of 35 g to be predictive of markedly increased malignancy risk. Pulsed, intravenous, cyclophosphamide regimens have less haemorrhagic cystitis and total cyclophosphamide exposure and are likely to be associated with lower bladder malignancy risks.
Take home points

1. Vasculitis is an avoidable cause of ESRD, and ESRD is usually the result of a delayed diagnosis.
2. ANCA-associated renal vasculitis is a common cause of unexplained acute renal failure in the elderly.
3. A prodromal phase of flu-like symptoms, weight loss and polymyalgia usually precedes a diagnosis of ANCA vasculitis by several months.
4. There should be a high index of suspicion for vasculitis in the presence of persisting unexplained constitutional symptoms or focal signs of inflammation, such as, arthritis, episcleritis or chronic ENT disease.
5. Active renal vasculitis is always accompanied by haematuria and proteinuria. Their absence reliably excludes this diagnosis.
6. Rituximab is an alternative induction therapy to cyclophosphamide, especially when treating relapsing or refractory disease.
7. Plasma exchange increases rates of renal recovery in severe presentations and is also used for alveolar haemorrhage.
8. Following successful remission induction, prolonged remission maintenance therapy is required to prevent relapse. Azathioprine is more effective than mycophenolate mofetil and preferable to methotrexate when there is renal impairment.
9. ANCA testing has a role in predicting relapse risk and a positive ANCA is more closely associated with relapse after treatment withdrawal.

References

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest


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** The validation of the efficacy of intravenous cyclophosphamide for newly diagnosed patients with renal vasculitis.


* Evaluation of cyclophosphamide in those with severe renal vasculitis.

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Chapter 14
Polyarteritis nodosa: Clinical characteristics, outcome, and treatment
Loïc Guillevin

Introduction
Polyarteritis nodosa (PAN) was the first vasculitis to be described by Küßmaul and Maier.\(^1\) For many years what are now known to be distinct vasculitides were then considered together under the term PAN. The last to be separated from PAN were Churg–Strauss syndrome, a vasculitis occurring in asthmatic patients,\(^2\) and microscopic polyangiitis (MPA), individualized from PAN by Wohlwill\(^3\) then redefined by Davson et al.\(^4\) Today, PAN is a well-defined vasculitis that affects medium sized vessels. Considering PAN aetiologies, primary and secondary forms can also be discerned, as PAN can be the consequence of hepatitis B virus (HBV) infection,\(^5,6\) and sometimes of other aetiological agents.\(^7–9\) In this chapter, we review the main characteristics of PAN, its outcome and treatment. PAN histology and pathogenesis have been extensively detailed in other chapters of this book.

Classification
PAN classification criteria are detailed elsewhere. Nevertheless, we would like to focus on some pertinent points. PAN and MPA were, finally, individually characterized in the Chapel Hill Consensus Conference Nomenclature.\(^10\) This distinction had not been made apparent in the classification criteria\(^11\) developed in 1990 by the American College of Rheumatology (ACR) because some of their clinical manifestations are very similar. Nevertheless, major differences exist. PAN affects medium sized vessels and MPA small sized vessels, especially arterioles, capillaries and venules. MPA is responsible for glomerulonephritis and lung capillaritis; PAN is characterized by vascular nephropathy and never affects the lungs. MPA is one of the anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides, together with Wegener’s granulomatosis and Churg–Strauss syndrome. Those autoantibodies yield a fluorescent peri-nuclear-labelling pattern and enzyme-linked immunosorbent assay (ELISA) almost always shows their anti-myeloperoxidase specificity. The majority of MPA patients are ANCA positive, especially more than 80% with glomerulonephritis and/or alveolar haemorrhage.\(^12\) In contrast, ANCA presence is an exclusionary criterion for PAN.\(^13\)
Characteristics

Epidemiology

PAN is a rare disease. In a study that considered only biopsy-proven forms, its annual incidence and prevalence were, respectively, 0.7/100000 and 6.3/100000 inhabitants. Estimates of the annual incidence rate for PAN-type systemic vasculitides in a general population range from 4.6/100000 in England, 9.0/1000000 in Olmsted County, Minnesota, to 77/1000000 in a hepatitis B-hyperendemic, Alaskan Eskimo population. In Seine–Saint-Denis county (a Paris suburb), PAN prevalence was estimated at 24/1000000 inhabitants in 2000.

For a minority of patients, infections, mainly viral, have been recognized as being responsible for PAN. Indeed, a close relationship has been demonstrated between PAN and HBV infection. In France, contamination due to an infected blood transfusion has now disappeared, and intravenous drug use is also less frequent than 20 years ago. Sexual transmission is one of the main routes for infection transmission. The development of vaccines against HBV and their administration to people at risk explain the sharply decreased number of new cases observed since 1989. In the past few years, the frequency of HBV-related PAN (HBV–PAN) has declined to 7.3%. For the last 5 years, fewer than five patients a year have been identified throughout the country. The majority of these new patients seen in recent years came to France from overseas countries, where the prevalence of HBV infection remains high. This viral infection has also changed, with the occurrence of more mutant viruses and fewer wild-type HBV strains.

Some other viruses have been associated with PAN onset but they could only explain several cases. HCV prevalence in our patients was low, below 10% and confirmed our previous findings. GBV-C virus, when sought in PAN patients, has not been considered to be an agent responsible for the vasculitis. Although a few cases of PAN attributed to erythrovirus (previously parvovirus) B19 infections have been described, a systematic survey of PAN patients did not show a higher prevalence of this virus in patients than the control population. Other viruses have been incriminated as causing PAN, including anecdotal cases of human immunodeficiency virus infections.

In addition to infections, PAN has been described in association with malignancies, mainly haemopathies. The closest relationship has been established with hairy-cell leukaemia.

Clinical features (Table 14.1)

Age and sex

PAN can be observed in any patient, independently of age. It usually appears around 50 years and has a male predominance, but can also develop in children and patients older than 65.

General symptoms

Poor general condition is noted in two out of three patients, early during the course of the disease, and can be the sole manifestation. Every type of fever can be observed and a muscle biopsy can make the diagnosis in these febrile patients.
The patients usually complain of myalgias that are intense, diffuse, spontaneous or induced by pressure. Arthralgias predominate in the major joints: knees, ankles, elbows and wrists, but are rarely present in shoulders and hips. Pain localized to nerve territories can be present. Muscle wasting can reflect the presence of weight loss, sometimes exceeding 20 kg, and paralysis. Patients can be bedridden due to the intensity of pain and amyotrophy.

**Neurological manifestations**

Peripheral neurological symptoms are frequent, whereas central nervous system (CNS) involvement is more uncommon.

**Peripheral neuropathy**  Motor, sensory or sensory–motor peripheral neuropathy, mainly distal and asymmetrical, is the most frequent neurological manifestation of
PAN, observed in around 70% of the patients. Mononeuritis multiplex is common. The most frequently involved nerves are superficial peroneal, deep peroneal, radial, cubital and/or median nerves. Paralysis occurs early, usually during the first trimester. Pertinently, peripheral neuropathy can be the first manifestation of PAN, as it was for 10% of the cases described by Cupps and Fauci, and was observed in 25% of our patients. Pain, paresthesias and, more rarely, segmental oedema may precede paralysis.

Sensory symptoms can be predominant, mostly hypoesthesia. Deep sensory transmissions are never affected. The electromyogram is characteristic of truncular axonal neuropathy. Moreover, electromyography usually shows that the extent of neuropathy is larger than expected based on the clinical manifestations. Symmetrical neuropathy is observed less frequently.

Several peripheral neuropathy flares may occur and they cannot be predicted. Neurological symptoms regress slowly under treatment. Twelve to 18 months are often necessary to obtain optimal recovery and evaluate the extent of sequelae. Sensory symptoms persist longer, sometimes definitively. Cranial nerve palsies are rare and occurred in around 1% of our patients. Cranial nerves III, VI, VII and VIII may be affected. Cerebrospinal fluid analyses are usually normal but, in a few cases, the protein level can be elevated, without cells.

**CNS involvement** CNS involvement is rare. Seizures, focal or generalized, haemiplegia and brain haemorrhage can be seen. The central manifestations differ according to the location and mechanisms involved: brain arteritis, aneurysm rupture or haematoma. Cognitive dysfunction may be the first manifestation of angiitis and regress under treatment. Computerized tomography scans are usually normal but magnetic resonance imaging (MRI) shows T2-weighted hypersignals in the brain, localized to the white matter. Although not specific, they evoke the diagnosis. Brain angiography is done less frequently as MR angiography (MRA) has become the technique of choice. Both can show calibre irregularities orienting the diagnosis. Every brain territory can be involved.

Ischaemic or haemorrhagic seizures can also be the consequence of malignant hypertension, which has become very rare since effective antihypertensive drugs became available and are prescribed. Distal inflammation with subsequent stenoses and/or thromboses leading to obliteration of spinal vessels can be responsible for CNS symptoms. Sphincter dysfunction may be observed and is probably underestimated.

**Renal manifestations** Vascular nephropathy can be responsible for renal insufficiency of variable intensity. Severe or malignant arterial hypertension may occur as a complication. Acute renal failure occurs early during the course of PAN or at the time of a flare. Some patients may require renal dialysis during the early phase or later, when renal failure occurs as a consequence of chronic renal ischaemic deterioration. The outcome of renal insufficiency cannot be predicted and improvement may occur. Some patients may be able to come off dialysis but end-stage renal failure may develop years after the early manifestations of PAN.

In patients with renal involvement, angiography, when performed, shows renal infarcts, multiple stenoses and microaneurysms of branches of digestive and renal arteries.
Renal infarcts are responsible for renal insufficiency. Microaneurysms rupture rarely, spontaneously or after renal biopsy. Renal haematoma can be extensive and requires embolization and even nephrectomy should it fail.

**Orchitis**

This is a rare but characteristic manifestation of PAN. It was retained as one of the ACR classification criteria. Non-infectious orchitis is rarely the first manifestation affecting the testicular artery. When treated immediately, orchitis may regress under steroids. Exclusive testicular involvement evokes a tumour or testicular torsion and histological examination is able to make the diagnosis. In our experience, orchitis was often present in HBV–PAN but no close relationship could be demonstrated between the viral infection and testicular manifestations.

**Skin manifestations**

Vascular purpura is less frequent in MPA than in PAN. Skin nodules can be present because they contain medium sized vessels.

Skin manifestations are predominantly located on the legs. Nodules are small, ranging in diameter from 0.5 to 2 cm, and are found in the dermis and hypodermis. They appear and disappear within a few days. Racemosa or reticularis livedo can be observed. Post-inflammatory ischaemic leg ulcers can arise and are recognized by their topography. When they occur in patients with atheroma, a differential diagnosis with cholesterol emboli should be discussed. According to the literature, half of the patients developed at least one episode of skin involvement. Nevertheless, in the majority of those studies, PAN and MPA were considered together and most cutaneous manifestations should probably be attributed to MPA.

**Peripheral vascular manifestations**

Arterial obstruction is responsible for distal digital gangrene. Angiography can demonstrate the presence of stenoses and/or microaneurysms. Raynaud’s phenomenon, when present, can remain isolated or be complicated by necrosis. In some cases, type II or III cryoglobulinaemia can be present. Although cryoglobulinaemia is usually detected in the setting of HCV infection, and not PAN, it can occur in HBV–PAN, in which case, it disappears after treatment.

**Lung manifestations**

The lung is not affected by PAN. Histological studies showed that bronchial artery vasculitis can be present but is asymptomatic. When pulmonary symptoms occur, infections should be sought and are usually found.

**Gastrointestinal involvement**

Gastrointestinal tract involvement is one of the most severe manifestations of PAN, especially in the case of HBV infection. Abdominal pain occurs in one-quarter to one-third of the patients and can be the first symptom. In a majority of patients, ischaemia of the small bowel is present but rarely the colon or stomach. Small intestine perforation and digestive bleeding are the most severe manifestations. Gastric perforations are rare, as are those of the oesophagus.
Relapses after surgery or medical treatment are signs of poor prognosis. Digestive malabsorption and acute or chronic pancreatitis with pseudo-cysts have been described; their prognoses are extremely dismal. Vasculitis of the appendix or gallbladder is sometimes the first PAN symptom; its significance is not equivocal: it is sometimes a pathological curiosity without any other clinical, pathological and/or immunological involvement of vasculitis. In other cases, cholecystitis or appendicitis is another symptom of PAN. The prognoses of these manifestations seem different, depending on whether one or the other is the first sign of PAN or a complication of previously diagnosed and treated PAN. In the former situation, the prognosis remains good; however, when these symptoms occur during the course of PAN, they often precede other severe symptoms of gastrointestinal involvement and the prognosis is poor.

Liver involvement, such as infarction and haematomas, can exist, even in the absence of HBV infection.

Cardiac manifestations

Cardiac manifestations are due to vasculitis of the coronary arteries or their branches, or to severe or malignant hypertension. In autopsy studies, histologically observed cardiac manifestations, mainly affecting the myocardium, were found in 78% of patients, and radiological and electrocardiogram abnormalities in 40%. In our experience, despite coronary artery vasculitis, angina is rare and coronary angiography is usually normal. Specific myocardial involvement is the sequential consequence of inflammation, stenosis and/or thrombosis and, finally, coronary artery occlusion. Stenosis(es) can be seen in the main coronary arteries, as described by Küssmaul and Maier (nodular coronary arteritis), and were present in 25/66 autopsies performed by Holsinger et al. Although coronary aneurysms sometimes occur, ruptures are rare. Most cases have been described in infants and, retrospectively, we postulate that most of them could be due to Kawasaki disease. Nonetheless, aneurysms cannot be excluded in adults, even though we must admit never having seen one in our specialized referral centre. Arterioles can also be affected and foci of myocardial necrosis can be seen.

Left heart failure is the most frequent manifestation of cardiac involvement. When cardiac insufficiency is present, it occurs early during the course of PAN. Heart enlargement was observed in a quarter of the patients in a reported series. Atrioventricular block, like severe ventricular rhythm disturbances, is extremely rare. Supraventricular rhythm disturbances are more frequent than ventricular rhythm disturbances. The vasculitic process more rarely affects the pericardium and pericarditis is usually a non-specific satellite of myocardial involvement. Pericardial involvement is rare and asymptomatic. However, pericarditis can be the first manifestation of PAN and its biopsy can make the diagnosis. Biological markers, such as brain natriuretic peptide (BNP) or its precursor protein N-terminal proBNP (NT-proBNP), could contribute to an early diagnosis of cardiac insufficiency and troponin I to look for myocardial involvement. Imaging techniques also have a major role to play, not only echocardiography, but also MRI, which detects myocardial signals of vasculitis and is able to study precisely cardiac function parameters and visualize pericardial and myocardial involvements. No literature on PAN is available but such techniques are already being used in Churg–Strauss syndrome and other vasculitides.
Arterial hypertension
Hypertension is present in 34–36% of PAN patients and is usually mild; however, it should be kept in mind that it can be triggered or adversely affected by steroids. Malignant hypertension was detected in 6/115 (5.2%) of our HBV–PAN patients and 11/125 (4.9%) patients without HBV infection. Hypertension is more frequent in HBV–PAN. It responds well to angiotensin converting enzyme inhibitors, which improved its prognosis.

Miscellaneous
Periosteal modifications of leg bones are rarely seen. Ophthalmological signs have been described in PAN, some of which are severe, like uni- or bilateral retinal detachment and retinal vasculitis. Splenic infarcts and splenic rupture have been described. Specific gingivitis, breast involvement, and affected uterine arteries have been described anecdotally. However, concerning the former, it could be thought that this vasculitis involved smaller arteries than those of PAN and might have been MPA or even Wegener’s granulomatosis.

HBV–PAN
The immunological process responsible for this PAN subgroup usually becomes manifest less than 6 months after infection. Hepatitis is rarely diagnosed and remains silent before PAN onset. Over the past few years, we observed that some patients developed PAN several years after infection and hypothesize that these cases are caused by HBV mutants. Clinical manifestations are roughly the same as those commonly seen in PAN, but with several differences: malignant hypertension (6%), renal infarction (28%) and orchiepididymitis (25%) were more often associated with HBV infection, and might reflect a more pure group of PAN. These manifestations occur in patients 50 years old with acute disease. Seroconversion usually leads to recovery. Sequelae are the consequence of vascular nephropathy but, even in patients with renal insufficiency, it is possible to obtain recovery with little residual impairment of renal function.

Regarding other symptoms, abdominal manifestations (53%) were common, especially surgical emergencies. Among the nine patients studied by Sergent et al., two of the three deaths were attributed to colon vasculitis. Furthermore, 31% of Eskimo patients described by McMahon et al. died, and one of the four early deaths was the consequence of bowel perforation. In our series, 41/115 (35.6%) patients died, seven of gastrointestinal involvement (6%). Hepatic manifestations of PAN are clinically moderate. Hepatic cytolysis is moderate in most cases and cholestasis is minor or absent. When liver biopsies were obtained, they frequently showed chronic hepatitis, even in PAN, which occurred only a few months after HBV infection.

Laboratory tests and angiographic investigations

Biological analyses
Inflammatory signs are found in more than 80% of the patients. Hypereosinophilia >1500/mm³ is rare. HBs antigen should be systematically sought, even though it was found in only one-third of the patients.
ANCA are not detected in the sera of PAN patients and we consider that, in the context of systemic vasculitides, the presence of peri-nuclear-labelling P-ANCA, with anti-myeloperoxidase specificity in ELISA, should be considered exclusionary for ‘classic-PAN’ and a diagnostic argument in favour of MPA. 

**Angiography**

Angiography is able to visualize microaneurysms and stenoses (narrowing or tapering) in medium sized vessels. They are not pathognomonic but are frequently present in PAN. Arterial saccular or fusiform aneurysms range in size from 1 to 5 mm and are predominantly seen in the kidneys, mesentery and liver. These lesions may disappear with arteritis regression. Angiography is a useful diagnostic tool when other diagnostic examinations are negative, especially in a context of abdominal pain and nephropathy. In our opinion, the presence of microaneurysms should orient the classification of the vasculitis towards PAN.

**Outcome and prognosis**

**Relapses**

PAN is a disease that relapses more frequently in the absence of HBV infection: less than 10% of HBV–PAN patients versus 28% of non-HBV–PAN patients. At present, it is still not possible to predict the subgroup of patients who will relapse or the severity of those relapses. The clinical relapse pattern does not necessarily mimic the original presentation, as entirely new organs can be involved at relapse.

**Deaths**

The causes of deaths can be divided into two categories: related to vasculitis manifestations or treatment side effects.

**Deaths related to the vasculitis**

In all vasculitides, when major organs are involved, lethal complications can and do occur. A few patients die early from multi-visceral involvement and treatment is unable to control their disease. Death occurs during the course of PAN characterized by fever, rapid weight loss, diffuse pain and one or several major organ involvement(s). It often occurs during the first months after disease onset and is often the consequence of gastrointestinal involvement.

**Deaths related to treatment side effects**

Side effects are frequently responsible for deaths. Deaths occurring during the first months of the disease are often due to uncontrolled vasculitis; fatalities during the following years may be the consequence of treatment side effects. Infections are the primary cause of death and are favoured by steroids and/or cytotoxic agents, as was shown in our patients. Septicaemia frequently occurs during the first months of treatment and is the consequence of the intense induction therapy. Reductions of treatment doses and durations could contribute to diminishing such
complications and novel therapeutic strategies are being tested to achieve them while enhancing efficacy. Viral infections occur usually later. *Pneumocystis jiroveci* pneumonia has become a rare event since the systematic implementation of co-trimoxazole prophylaxis.72

**Treatment**

In this section, the reader should be aware that the results of most of the ‘oldest’ published series concerning PAN treatment and outcome in fact considered two separate entities, PAN and MPA,30,31,73 and, sometimes, Churg–Strauss syndrome as well.74,75

To help the clinician choose the most effective therapy and avoid overtreatment, we devised the five-factor score (FFS),76 which has significant prognostic value, and parameters, defined as follows, were responsible for higher mortality: renal insufficiency (creatininaemia >150 μmol/l), cardiomyopathy, gastrointestinal manifestations, age >65 years old, and absence of ear, nose and throat (ENT) involvement. When FFS at diagnosis was 0, 1 or ≥2, mortality at 5 years reached 9%, 21% or 40%. Although it has not been demonstrated that treatment should be chosen as a function of these criteria, it seems probable that the FFS should be considered in the therapeutic strategy.

**Indications of corticosteroids alone**

Steroids alone are effective when prescribed to treat PAN without poor prognosis factors, i.e. FFS = 0,77 and obtained survival rates similar to those of patients whose regimen combined corticosteroids and cyclophosphamide. Based on the results of this CHUSPAN trial,77 we were able to show that remission could be obtained with corticosteroids alone and that relapses or systemic necrotizing vasculitides unresponsive to steroids alone could benefit from the adjunction of an immunosuppressant (cyclophosphamide or azathioprine).

**Indications of corticosteroids and cyclophosphamide**

The prognosis of non-HBV–PAN has been transformed by corticosteroids and immunosuppressants, especially cyclophosphamide. Corticosteroids alone were able to increase the 5-year survival rate from 10% for untreated patients to about 55% in the mid-to-late 1960s. Survival was further prolonged by adding an immunosuppressant, either azathioprine or cyclophosphamide, to the treatment regimen.

**Cyclophosphamide**

When cyclophosphamide is indicated for PAN patients, an intravenous pulse should be preferred to oral administration, as it achieves a more rapid clinical response, which is particularly important for patients with active disease. When combined with corticosteroids, intravenous cyclophosphamide should not exceed 12 pulses. At present, we recommend pulse cyclophosphamide until remission is obtained and then prescribe 12–18 months of maintenance therapy, with azathioprine or methotrexate, as has been demonstrated also in ANCA-positive systemic necrotizing vasculitides.78
Treatment of HBV- and other virus-related-PAN

Virus-associated vasculitides require specific treatments. In the context of chronic hepatitis B, corticosteroids and immunosuppressants can effectively treat vasculitis and the short-term outcome is comparable to strategies comprising plasma exchange (PE) and anti-viral agents. However, immunosuppressants have deleterious effects: they enhance virus replication, and, over the long term, they perpetuate chronic HBV infection and facilitate progression towards cirrhosis, which may be complicated later by hepatocellular carcinoma.

Based on the efficacies of anti-viral drugs against chronic hepatitis and PE for PAN, we combined the two therapies to treat HBV–PAN. The rationale of the therapeutic sequence was for initial corticosteroids to rapidly control the most severe life-threatening PAN manifestations, which are common during the first weeks of the vasculitis, and for their abrupt withdrawal to enhance immunological clearance of HBV-infected hepatocytes and favour HBe-antigen-to-anti-HBe-antibody seroconversion, with PE to control the course of PAN.

A regimen combining an anti-viral agent (vidarabine, interferon-α2b or, more recently, lamivudine) and PE to treat HBV–PAN obtained excellent overall therapeutic results in a few weeks. The anti-viral strategy increases the HBe-antigen-to-HBe-antibody seroconversion rate from 14.7% with conventional treatment to 49.4% for patients receiving an anti-viral agent and PE.

Plasma exchange

Unlike ANCA-associated vasculitis patients with crescentic glomerulonephritis responsible for severe renal insufficiency (creatininemia >500 μmol/l), for whom PE can improve renal function, there is presently no argument to support the systematic prescription of PE at the time of diagnosis of non-HBV–PAN, even for patients with poor prognosis factors. A prospective trial organized by the EUVAS group confirmed that PE were superior to pulse corticosteroids to improve renal function significantly but had no effect on survival. However, PE are a useful tool, as second-line treatment of PAN refractory to conventional therapy.

General considerations

Specific treatments for hypertension, pain and motor rehabilitation are also important elements in the overall treatment regimen of PAN patients. As maximal immunosuppression is given at treatment onset, prevention of opportunistic infections, like Pneumocystis jiroveci pneumonia, may be necessary and should be prescribed on an individual basis. In the case of gastrointestinal involvement with persistent abdominal pain, despite medical treatment, exploratory surgery should be performed to look for and treat bowel perforation masked by the corticosteroid and immunosuppressant regimen. For these patients, it seems reasonable to administer drugs intravenously to circumvent possibly impaired drug absorption. Rapid and severe weight loss due to severe gastrointestinal involvement must be countered with parenteral nutrition. Despite the fact that weight loss has not been demonstrated to be a factor of poor prognosis, good general condition is always preferable, because it contributes to limiting the infection rate under cytotoxic agents.
References

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest


Chapter 15

Vasculitis (ANCA negative): Henoch–Schönlein purpura

Rosanna Coppo and Alessandro Amore

Definition

According to the 1994 Consensus Conference on Nomenclature of Systemic Vasculitis, Henoch–Schönlein purpura (HSP) is a small vessels vasculitis (involving capillaries, arterioles, venules) with immunoglobulin (Ig)A-dominant immune deposits in small vessels, involving skin, gut and glomeruli and associated with arthralgias or arthritis.\(^1\) First identified by Heberden, the purpuric and articular manifestations were described by Schönlein and the gastrointestinal and renal features by Henoch. The combination of various systemic and renal symptoms leads to apparently different clinical entities that often overlap with that of autoimmune diseases. HSP needs to be differentiated from cutaneous allergic reactions to drugs, and infectious agents. In the past this led to designation such as hypersensitivity angiitis, anaphylactoid and rheumatoid purpura or streptococcal rheumatic peliosis.\(^2\)

Clinical and laboratory features

Diagnostic criteria

The most powerful diagnostic criterion is given by skin biopsy, showing granulocytes in the walls of small arterioles or venules (leucocytoclastic vasculitis) and/or IgA deposits in small vessels.

Epidemiology and enhancing factors

HSP is a relatively uncommon disease particularly in adults, whereas in children its incidence is about 14/100000 cases/year. It has a 2/1 male preponderance. In children, HSP is the most frequent vasculitis.\(^3\) The median age at onset is about 4 years, although it can affect the elderly.

In unselected cohorts of children, the prevalence of the renal involvement during the course of HSP varies from 20% to 54% (mean 33%), whereas in adults this frequency is much higher (mean 63%).\(^4-6\) Despite the possibility that the mildest cases of renal involvement among children could be underdiagnosed, and that some adult patients could be misdiagnosed primary vasculitis, the more frequent development of renal disease in older cases remains unquestionable and unexplained.

The geographical distribution of HSP is similar to that of primary IgA nephropathy (IgAN), as the syndrome is common in Europe, particularly in France, Italy, Spain,
UK and Finland, and in Asia, mostly in Japan, Singapore and China, whereas it is less common in North America and Africa. HSP is rarely detected among black people and Indians.

Triggering factors are reported in about two-thirds of the cases, mostly infections and particularly in children. *Streptococcus β, Helicobacter pylori, Yersinia, Mycoplasma, Toxoplasma*, Varicella, measles, Rubella, adenovirus, HIV and several other agents have been sporadically recorded among the precipitating factors, but without evidence of causality. The peak incidence of HSP is in winter to spring. A coincident role of allergic reactions to vaccinations (against smallpox or influenza), drugs (including ciprofloxacin, vancomycin, minocycline, carbazepine and others) or other allergens has been strongly suspected in several cases. Some familiar cases and restricted epidemic clusters of HSP have been observed.

**Systemic extra-renal manifestations**

The skin lesions are characteristic and consist in red-purple slightly raised ‘palpable’ purpuric macules that do not disappear on pressure and are not related to thrombocytopenia. Fever and general malaise may accompany the rash. At the beginning the picture is hardly distinguishable from infectious purpuras or allergic reactions. HSP purpura mainly involves initially the lower extremities and buttocks, becoming generalized in some cases. Haemorrhagic bullous lesions seldom develop on body areas under moderate dress pressure. The typical HSP lesions consist of a leucocytoclastic vasculitis of dermal vessels. Relapses of purpura are very frequent, in almost a third of patients, and may occur up to 10 times during follow-up.

Gastrointestinal symptoms are reported in 50–78% of all cases, more frequently in children. Abdominal manifestations include diffuse abdominal pain, increasing after meals, referred to as ‘bowel angina’ and often accompanied by vomiting, haematemesis and rectal bleeding or melena. In some cases, the pain is so severe to mimic a surgical emergency, although intussusception, intestinal infarction, bowel perforation, which may require surgical intervention may develop on rare occasions. HSP may present with acute abdomen without typical skin manifestations, and gastroscopy and colonoscopy can be helpful in the early diagnosis of HSP, detecting diffuse mucosal oedema, erythema, petechiae or multiple irregular ulcers, especially in the second portion of duodenum and in the terminal ileum.

Transient arthralgia, due to oligo-articular synovitis, mostly involving lower limb joints, are reported in 50–70% of all cases with light prevalence in children. These lesions do not evolve into joint erosions or deformities. Rare complications include pulmonary, cardiac, pancreatic, genital and neurological symptoms. In these cases, mostly with fatal course, there is the possibility of polyangiitis overlap syndrome. Children, more frequently than adults, present with systemic extra-renal clinical pictures of particular severity.

**Renal manifestations**

The development of renal lesions is generally unrelated with extra-renal signs. The incidence and severity of clinical renal manifestations represents referral patterns and case selection. Paediatricians report a systemic disease with modest and transient renal
damage, whereas nephrologists describe much more severe renal involvement both in children and in adults. The multi-centre study of the Italian Group of Renal Immunopathology focused on HSP patients with a renal disease severe enough to warrant renal biopsy. The number of patients enrolled, representative of both childhood and adulthood (136 adults and 83 children), the length of follow-up (median 4.5 years, up to 20 years) and, mostly, the homogeneity of the inclusion criteria have provided data of some interest. Even though the findings of this study cannot be generalized, as less severe cases not needing renal biopsy were not included, it allowed a direct comparison of adults and children with common enrolment criteria.

The renal manifestations of HSP range from isolated microscopic haematuria to gross haematuria and mild proteinuria to nephrotic syndrome. Renal function is often normal at presentation, particularly in children, but sometimes there is a renal impairment at onset and rarely progressive renal insufficiency. Moderate renal impairment due to an acute nephritic syndrome, often with hypertension is observed in one-third of the cases who need renal biopsy. Isolated microscopic haematuria is the most frequent clinical presentation of HSP nephritis in unselected patients with HSP, particularly in children, and it is often transient. When haematuria persists, the nephritis become chronic, and proteinuria often develops. In unselected series of children, the nephrotic syndrome is detected slightly less frequently than in adults (children 8–32%, adults 16–40%).

Palpable purpura often precedes or is coincident with the onset of nephritis; but in 10% of patients purpura follows renal symptoms by weeks or months, leading to initial diagnosis of idiopathic IgAN. These observations confirm the similarity between idiopathic IgAN and HSP. However, it is interesting that macroscopic haematuria coincident with upper respiratory tract infections, so common in IgAN patients, is very rare in HSP.

In children below the age of 5 years, haematuria can be due to haemorrhagic ureteritis. In these cases haematuria is generally associated with loin and renal colic pain. Ureteric lesions, when healed in fibrosis, may progress to ureteral stenosis and ureteral obstruction, often requiring surgical correction.

Serum abnormalities and genetics
Mean levels of serum IgA are increased, as in idiopathic IgAN, but the increase is often limited to the acute initial phase, and when the disease heals, in benign cases, serum IgA returns within normal values. The subclass mostly increased is polymeric IgA1. IgA1 immune complexes (IgAIC) or mixed IgA1/IgGIC of IgA/fibronectin aggregates have been detected in circulation, mostly during the acute phases or during relapses. Serum IgA1 molecules present with an aberrant glycosylation in both primary IgAN and HSP. IgA1 is highly glycosylated, with O-short carbohydrate chains based on N-acetyl galactosamine (GalNac) residues usually extended with galactose (Gal) and covered with sialic acid. In HSP and in idiopathic IgAN, IgA1 molecules have a defective galactosylation and sialylation with increased exposure of internal GalNac residues. Anti-glycan IgG antibodies have been recently reported, mostly in cases with renal involvement. Desialylated and degalactosylated IgA has increased reactivity with several endogenous or exogenous antigens, including IgA rheumatoid factor,
anti α galactosyl antibodies, mesangial cell antigens and mesangial matrix. We observed a direct glycan-based interaction (lectin binding) due to overexpression of internal sugar residues, more than true antigen-specific antibody production. High levels of IgA reacting with sonicated neutrophil extracts (IgA-ANCA) and with purified cytoplasmatic antigens (myeloperoxidase) have been detected in children with HSP nephritis. The presence and the meaning of IgA-ANCA is still debated, and lectin-like interactions are likely to play a role in this reactivity. However, in some patients particularly those with severe renal or gastrointestinal involvement, true IgG-ANCA have been detected.

Serum C3 and C4 values are within the normal ranges, even though CH50 and properdin levels are often reduced. These data, together with the frequent increase in serum C3d we detected in adults and children suggest a subtle C3 activation, possibly via the alternative pathway, but this is balanced by enhanced complement synthesis.

Abnormalities of T suppressor activity are reported in the acute phase. Transforming growth factor (TGF) β-secreting T cells have been detected during the phases of clinical activity of HSP, which resolved during recovery. Plasma IgE levels are increased in HSP, and significantly higher than in IgAN. This increase could be consequent to a prevalence of Th2 lymphocytes. Serum eosinophil cationic proteins are elevated in HSP, confirming an activation of the IgE-system allergy.

No significant abnormality of the coagulation cascade is detectable, as the purpura is due to vascular damage. Platelet count is in the normal range and the activity of the clotting factors is normal. Abnormalities in fibrin-stabilizing factor (factor XIII) have been reported as well as increased von Willebrand factor plasma levels, indicating endothelial damage that favours fibrin deposition.

A possible genetic predisposition to HSP has been suggested by the increased frequency of HLA-BW35. In Europe an association with DRB1*01 and DRB1*11 (64% versus 48% in controls) has been reported. A higher prevalence of C4 gene deletions has been reported in Japanese patients than in controls.

Pathology

Light microscopy

HSP nephritis is characterized, as idiopathic IgAN, by mesangial damage with different degrees of hypercellularity, with changes ranging from focal-segmental endocapillary proliferation to crescent formation. These lesions are extremely variable among patients and during the course of the disease in the single case. Different classifications consider the severity of the proliferative intra- and extra-capillary lesions. Meadow et al. considered the degree of mesangial proliferation, with endo-extra-capillary extension. Emancipator et al. distinguished six histological classes according to presence/absence and extension of extra-capillary proliferation, with subclasses defining the characteristics of the endo-capillary lesions. More recently, a simpler classification has been proposed by Pillebout et al. (Table 15.1). Distinction between acute and potentially reversible or chronic lesions can provide a useful guide to treatment.

The segmental proliferative lesions frequently show adhesions of the tuft to parietal epithelium and sometimes there is splitting and duplication of glomerular basal membranes. Rarely, this feature mimics membranoproliferative glomerulonephritis (GN).
Focal fibrinoid necrosis is often present at onset, and it corresponds, at a later time, to disorganized sclerosis. Intracapillary thrombi can be observed.

Degenerative tubular alterations with flattening, vacuolization, loss of the brush-border microvilli and focal atrophy are frequently detected. A lymphomonocytic interstitial infiltration characterizes progressive cases. Blood vessels may show medial hypertrophy and intimal fibroelastosis. Hyalin change and/or accumulation of fibrinoid material, or necrosis with inflammatory infiltration and clear findings of vasculitis can be present. In the past, these lesions were considered of diagnostic value; nevertheless, the presence of capillary necrosis even in idiopathic IgAN has invalidated this criterion.

The cohort of patients gathered by the Italian collaborative study showed a few cases with important extra-capillary proliferation. More than 50% of the biopsies of both adults and children did not have proliferative extra-capillary lesion. When present, these lesions involved less than 50% of glomeruli. In two-thirds of cases, the crescent formations were associated with endo-capillary proliferation. Necrosis of the capillary tuft was seldom present (in 10% of adults and 8% of children), coincident with extra-capillary proliferation. In some biopsies (2% of adults and 15% of children), peri-glomerular inflammatory infiltrates, mostly associated with crescents, were observed. Focal interstitial infiltrates were present in 10% of the cases. Tubular necrotic lesions were found in 15% of adults and 6% of children. In a very few biopsies there was a lymphomonocytic infiltrate in the vascular wall in the peri-arteriolar and peri-venular area.

**Immunohistochemistry**

The characteristic feature is granular mesangial IgA deposition, which, in contrast with the frequent focal and segmental proliferative changes, is always diffuse as in primary IgAN. IgA1 is the dominant subclass with equal distribution of light chains. The J chain is generally present indicating dimeric IgA. Extensive subendothelial deposits are associated with the most severe histological forms, with endocapillary proliferation and/or crescent formation.

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<tr>
<th>Table 15.1 Classification of Henoch-Schönlein nephritis lesions (data from Pillebout)</th>
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<tr>
<td><strong>Class 1</strong></td>
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<td><strong>Class 2</strong></td>
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<td><strong>Class 3</strong></td>
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<td><strong>Class 4</strong></td>
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<td><strong>Class 5</strong></td>
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As in idiopathic IgAN, C3 is co-deposited in 75–85% of the cases. The alternative complement pathway components and the membrane attack complex C5–C9, are regularly detected. IgG and IgM co-deposits are present in 40% of the cases. Fibrin/fibrinogen is frequent both in mesangial and in parietal areas, often coincident with mesangial proliferation.

In cases with severe glomerular changes, deposits of IgA and C3 can be found in arterioles and/or peri-tubular capillaries.

**Electronic microscopy**

Mesangial matrix expansion and variable degree of cellular hyperplasia are evident together with electron-dense deposits. These deposits are initially paramesangial and small in size (100–120 nm), and subsequently become larger (up to 800 nm) in the mesangial matrix. Sometimes, electron-dense deposit ‘humps’ with ‘garland’ shape or fluffy aspect are detectable. When deposited in the external rara lamina, they are delimited by a thin layer of new basement membrane.

**Extra-renal lesions**

The typical leucocytoclastic vasculitis with fragmented nuclei of leucocytes in and around arterioles, capillaries and venules, surrounded by infiltrating neutrophils and monocytes is detectable in the kidney and in other tissues, particularly in the skin and gut. Fibrinoid accumulations and arteriolar and venular necrosis are rarely found. Deposits of IgA and C3 are present in dermal capillary walls in purpuric lesions and uninvolved skin. Co-deposits of IgG and IgM can be present, whereas C1q and C4 are absent. Similar deposits have been reported in superficial dermal capillaries of IgAN patients. In dermatitis herpetiformis, IgA deposits are found as well, but they are located on the top of the dermal papilla. In systemic lupus erythematosus (SLE), the dermal–epidermal junction is mostly positive for IgG, C1q and C4.

**Clinico-pathological correlations at onset**

Patients with minimal proteinuria had higher prevalence of mild lesions, without crescents. In patients with significant proteinuria more severe renal lesions were frequently found, but with low predictive value for the single case. In children, particularly, cases with non-nephrotic proteinuria often had extra-capillary proliferation. Gross haematuria at presentation can be associated with crescent formations. Renal functional impairment at onset has a predictive value of severe histological lesions.

**Clinical course**

In most cases, particularly in children, HSP is often a self-limited condition with transient multi-organ involvement. The course of HSP nephritis is generally benign and the progression towards renal failure is estimated at around 2% in non-selected children admitted into general paediatric hospitals. In improving or recovered patients, sequential biopsies show regression of lesions, glomerular repair and disappearance of IgA deposits. Conversely, reference centres report remission rates below 50% and poor outcome in 10–25% of children, and HSP nephritis accounts for 2–3% of all
children on dialysis in Europe. In a long-term follow-up study of selected children, averaging 23 years, late progression was observed in 25% of children, even after initial clinical improvement.

The disease is more severe in adults, where the progression to renal failure is reported in 8–68% of cases. The outcome of patients selected on the need for renal biopsy is much more severe and long-term analyses show that 15–30% of patients progress to renal failure, with wide variability depending on the initial selection criteria and follow-up duration.

The cohort of patients enrolled in the Italian collaborative study provided information on the subgroup of patients with a renal disease severe enough to warrant renal biopsy. After 1–20 years (mean 5 years), one-third of cases were in remission, often complete and without significant urinary anomalies (Table 15.2). In another third of patients only minimal or moderate proteinuria was left. The outcome was substantially similar in adults and children. The time of progression to dialysis varied from a few days to 20 years, with an average of 3 years in adults and 10 years in children. The long-term renal survival of HSP nephritis in adults and children with an indication for a renal biopsy showed loss of renal function in 25% of cases after 10 years.

### Risk factors for the progression

As discussed above, in non-selected series of HSP nephritis older age is associated with a higher risk of progression, but not in biopsied patients. A good correlation between the clinical presentation and the long-term outcome is reported in paediatric series. In some cohorts nephrotic syndrome and/or renal insufficiency at onset were risk factors (44%) for renal failure after more than 25 years of follow-up. In the cohorts of biopsied patients of the Italian study, the most unfavourable prognostic factor was renal function impairment at presentation: 45% of adults with severe renal failure and 18% of those with moderate functional impairment eventually required chronic dialysis, versus only 2% of adults with normal renal function at onset. This association was not found in children, who experienced progression to renal failure even in cases with normal renal function at onset. Hypertension was a negative prognostic factor particularly in adults, in whom it was more constant and associated with renal function impairment. The predictive value of proteinuria showed different results in adults and in children. In both cohorts absent or mild proteinuria or, at the opposite end of the spectrum, nephrotic-range levels, were associated with high frequency of remission or

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<tr>
<th></th>
<th>Adults (%)</th>
<th>Children (%)</th>
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<tr>
<td>Clinical remission</td>
<td>32.5</td>
<td>31.6</td>
</tr>
<tr>
<td>Minimal or moderate proteinuria, normal glomerular filtration rate</td>
<td>32.7</td>
<td>42.1</td>
</tr>
<tr>
<td>Nephrotic proteinuria, normal glomerular filtration rate</td>
<td>3.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Moderate functional impairment</td>
<td>13.7</td>
<td>12.2</td>
</tr>
<tr>
<td>Severe functional impairment</td>
<td>2.1</td>
<td>5.3</td>
</tr>
<tr>
<td>Dialysis</td>
<td>15.8</td>
<td>7</td>
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deterioration, respectively, of renal functional deterioration. However, adult patients with moderate proteinuria seldom showed extra-capillary proliferation, whereas children with mild proteinuria frequently displayed severe histological lesions, with extra-capillary proliferation. Among adults, proteinuria >1.5 g/day predicted an unfavourable outcome. On the contrary, it was impossible to define a level of proteinuria in children associated with increased risk, as nephrotic and non-nephrotic children had a similar outcome. Multivariate Cox regression analysis demonstrated independent prognostic indicators of age at renal biopsy and mean proteinuria during follow-up. No other significant predictors at univariate analysis, maintained an independent predictive value at multi-variate analysis. The extent and activity of extra-capillary proliferation are recognized risk factors, particularly when crescents involve more than half of glomeruli. In the Italian cohort, almost all patients presented with crescents involving less than 50% of glomeruli. The predictive value of mild extra-capillary proliferation (renal failure in 39% of adults and in 18% of children with crescents) was not of statistical significance, as cases without crescents also experienced an unfavourable outcome (19% of adults and 23% of children).

**HSP nephritis and renal transplantation**

IgA mesangial deposits may recur in allografts, particularly in living-related transplant. The actuarial renal survival at 15 years is reported to be 80% in comparison with 82% in controls. The risk of recurrence is 35% at 5 years, being particularly high in those with necrotizing/crescentic glomerular changes in the native kidneys, with a loss of grafts in half.

**Therapy**

Mild cases without urinary signs or minimal microscopic haematuria, do not require treatment, particularly in children. Careful urine monitoring is needed to detect modifications in the clinical follow-up, mostly during the first 2–3 months after the purpuric rash. Extra-renal signs, mostly abdominal pain and arthritis, are generally controlled by small doses of steroids, which favour a rapid resolution. Cases with recurrent necrotizing purpura or heavy abdominal pain have benefited from intravenous infusions of immunoglobulin.

Attempts have been made to try to prevent the development of nephropathy by giving small–medium doses of prednisone (1–2.5 mg/kg/day for 1–3 weeks). Uncontrolled studies led to uncertain results, as a selection bias was likely. One prospective randomized controlled trial has suggested the benefit of 2 weeks of small doses of prednisone, but this has not been confirmed by more recent studies. Small doses of steroids given before the manifestation of renal signs are not considered to be able to prevent the development of severe and progressive nephritis, hence no indication exists.

Corticosteroids have been thought to be ineffective for treating established HSP nephritis. However, a selection bias favouring treatment of more severe cases was likely to have been introduced, as the severity of the disease was a major determinant in the decision to treat. Indeed steroids were proven to be effective in paediatric cases of HSP nephritis with severe endo-capillary and extra-capillary proliferation involving
more than 50% of glomeruli and clinical presentation of nephrotic or nephritic syndrome with impaired renal function. In these cases, pulses of methylprednisone, followed by several months of oral prednisone induced favourable results in 70% of patients versus 40% in untreated children. It is of interest to notice that in the same cohort, no effect of treatment was found when crescents involved less than 50% of glomeruli. Strong positive results have been obtained in severely crescentic forms with a combination of prednisone, azathioprine or cyclophosphamide. This consisted of triple therapy of 30 mg/kg intravenous pulses for 3 days followed by 6 months of prednisone and dipyridamole and cyclophosphamide for 3–4 months. More than 60% of these patients experienced a complete remission. Japanese studies also adopted heparin or warfarin in association with immunosuppressive drugs, reporting benefits, but no controlled study proved the benefit of anti-coagulation.

Plasma exchange in association with corticosteroids and cytotoxic drugs has been used in children with rapidly progressive HSP nephritis. Several cases had a remission with renal function improvement; however, most had subsequent renal relapses and, in spite of a new cycle of plasma exchange, patients progressed to end-stage renal failure.

In conclusion, overall analysis of the data reported by uncontrolled studies indicates that treatment with steroids (either intravenous pulses or oral therapy) or immunosuppressive drugs (cyclophosphamide or azathioprine) sometimes in association with anti-coagulation (warfarin or dipyridamole), are effective to lessen the progression to chronic renal failure in children with nephrotic-range proteinuria and/or important extra-capillary proliferation, provided that the therapy is initiated early enough, before a non-return stage characterized by the establishment of fibrous crescents and glomerular or interstitial changes.

Favourable results have been reported in potentially progressive patients with heavy proteinuria, by treatment with intravenous immunoglobulin infusions, even though rebound of clinical signs is observed after this treatment. Tonsillectomy has also been proposed for chronic HSP nephritis, as for primary IgAN, with the aim of limiting the mucosal immune response. Overall analysis does not support the recommendation for this intervention to treat HSP nephritis.

**Pathogenesis**

The renal lesions of HSP nephritis are indistinguishable to those of idiopathic IgAN and most nephrologists consider the two diseases as systemic or renal-limited forms of a single pathogenetical entity. Several reports support a common origin for the two diseases. These include the recurrence of IgAN without systemic signs in transplanted kidneys of patients with HSP nephritis and the development of HSP in a twin of a primary IgAN patient. Some children with HSP nephritis subsequently have episodes of macroscopic haematuria, without the other clinical features of HSP. Besides the mild and reversible form of HSP nephritis affecting children, when the disease becomes chronic and severe enough to warrant renal biopsy the histological lesions and the clinical outcome are similar to primary IgAN.

HSP nephritis was ascribed to the accumulation of IgAIC within glomeruli, as idiopathic IgAN. High levels of circulating IgAIC and IgA/fibronectin aggregate in
both conditions, although at higher levels in HSP nephritis.\textsuperscript{13–15} Over recent years attention has been focused on the carbohydrate moieties of IgA, and several data support the hypothesis of a defective immunoregulation leading to aberrant IgA glycosylation in patients with primary IgAN and also in HSP patients.\textsuperscript{16,17} Detection of IgG against degalactosylated IgA1 has favoured the hypothesis that anti-glycan antibodies may react, by means of a mimicry effect, with glycans expressed on the surface of viral or bacterial pathogens, leading to formation of mixed IgA/IgG circulating immune complexes. Notably, the same abnormality has been detected also in sera of patients with idiopathic IgAN. Although an imbalance in lymphocyte function, with a prevalence of Th2 over Th1 T cell subsets, can lead to altered IgA glycosylation, similar abnormalities could be derived from a defective activity of $\beta_{1,3}$ galactosyltransferase due to a congenital defect, or from de novo somatic mutations. No clear data are presently available in support of a genetic conditioning of aberrant glycosylation of IgA1 in patients with HSP or idiopathic IgAN. On the other hand, in cell lines isolated from patients with IgAN, but not in those from controls, cytokine stimulation reduced the expression of $\beta_{1,3}$-galactosyltransferase and its molecular chaperone Cosmc.

The reason why some patients with IgAN develop a systemic vasculitis and present with the full expression of HSP is a clue to the problem of the different pathogenesis of these two entities. Anti-neutrophil cytoplasm antibodies of the IgA isotype (IgA-ANCA) have been reported in adults with active HSP, but other reports were negative. The pathogenetic meaning of aberrant IgA glycosylation or of reactivity towards lysosomal antigens of leucocytes is still a matter of investigation. Aberrantly glycosylated IgA molecules show a high tendency to self-aggregation and escape the hepatic asialoglycoprotein receptor clearance. In addition, by virtue of enhanced lectin reactivity with fibronectin, laminin and collagen within the mesangial matrix they have a favoured renal deposition. The interactions with mesangial cell receptors may enhance the synthesis of a variety of cytokines, vasoactive factors and chemokines. In the pathogenesis of HSP nephritis a peculiar role could be played by complement activation as previously described. It is of interest that aberrantly glycosylated IgA can activate complement more efficiently than normal IgA through the lectin pathway initiated by mannose-binding lectin, favouring inflammation. Differences in complement activation by aberrantly glycosylated IgA might represent the distinct pathogenetic mechanism inducing the vasculitic lesions that differentiate patients with HSP from those with primary IgAN.

**Take home points**

1. A perfect diagnosis: IgA-dominant immune deposits in small vessels, involving skin, gut and glomeruli with clinical features of palpable purpura, associated with arthralgia and abdominal pain.
2. Renal involvement at onset presents mostly with haematuria and acute nephritic syndrome, with renal function impairment and proteinuria.
3. In children renal involvement is less frequent and less severe than in adults, moreover it often recovers in few weeks.
4. When renal involvement is severe and persistent over years, the long term prognosis of IgAN related to HSP is similar in children and adults.

5. Aberrantly glycosylated IgA1 circulating molecules are detectable in both HSP and primary IgAN: additional factors should favour the development of vasculitic lesions.

6. No prevention of severe renal involvement can be obtained administering prednisone when extra-renal signs only are present.

7. Short-term treatment with prednisone can control extra-renal signs when severe, particularly in presence of serious gastrointestinal involvement.

8. Risk factors for progression include severe proteinuria, extensive crescent formations and advanced chronic histological signs (tubular-interstitial damage).

9. Long-term therapy should be modulated according to clinical and histological features, ranging from prednisone alone in milder cases to alkylating agents (cyclophosphamide) and plasma exchanges in rapidly progressive ones.

10. After renal transplantation recurrence of IgA nephropathy occurs, whereas purpura bouts are extremely infrequent.

References

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest


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Takayasu arteritis (TA) is a chronic inflammatory arteriopathy of unknown aetiology that involves large vessels, e.g. aorta and its main branches and the pulmonary artery. This condition is named after Mikito Takayasu, a Japanese ophthalmologist, who described circular anastomosis of the retinal vessels in a young female in 1905.\textsuperscript{1} Schimizo and Sano recognized the clinical triad of absent radial pulses, hypersensitive carotid sinus and ocular fundal changes in 1948. The term Takayasu arteritis was introduced by Cacamise and Whitman in 1952. Other synonyms of TA are pulseless disease, aortic arch syndrome, occlusive thromoarteriopathy, middle-aortic syndrome, idiopathic medial aortopathy, aortitis syndrome, primary arteritis of the aorta, brachiocephalic arteritis, panaortitis, non-specific aortoarteritis and Onishi’s disease.

**Epidemiology**

TA has a worldwide distribution, but the prevalence in Asian and Central and South American countries like Japan, India, China, Korea, Thailand, Singapore, Israel, Peru, Columbia, Mexico and Brazil far exceeds that in the rest of the world.\textsuperscript{2} Studies from Sweden and USA estimated incidence rates to be 1.2 and 2.6 cases per million populations per year.\textsuperscript{3} Ethnicity is a significant factor in this disease. TA is rare among Caucasians. Asians are overrepresented in the TA population in USA.\textsuperscript{4} Most patients in France are from North Africa and the Antilles islands. A predominance of the mestizo race (partly of American Indian ancestry) has been reported among Mexican and Colombian patients.\textsuperscript{5,6} The gender distribution of TA is variable in different parts of the world. A marked female preponderance is encountered in Japan (8–24:1), Mexico (7:1), Korea (6:1), Brazil (5:1), Turkey (4:1), and China and Colombia (3:1), but the gender disparity is not so marked in India (1.5:1), Israel (1.8:1) and Thailand (2.2:1).

**Aetiology and pathogenesis**

The precise aetiology of TA still remains unknown. Hereditary, factors, infectious agents and hormonal and immunological perturbations have been implicated in the causation of this disease.

The geographical variation in the incidence and pattern of TA suggests a role for hereditary factors. Familial occurrence of TA including that in monozygotic twins has been reported. Association with several human lymphocyte antigen (HLA) alleles has been described. A close relationship has been noted between a specific variant of the
MHC class I chain-related (MICA) gene and TA. Those bearing MICA 1.2 showed a significantly greater risk of developing TA. Socioeconomic factors are also reported to influence the clinical features.

Infections such as tuberculosis and syphilis were considered to play a pathogenic role because of the histological similarity of TA with the granulomatous pathology of tuberculosis and syphilitic aortitis. Moreover, TA is encountered with increased frequency in countries where *M. tuberculosis* infection is endemic. Tuberculin positivity was noted in 81% of TA patients compared with 66% of the general population, and TA developed in close proximity to tubercular lymph nodes. Mycobacterial injection in aortic adventitia of rabbits was shown to create TA-like lesions. Subsequent studies, however, failed to demonstrate any microorganism in arterial specimens obtained at the time of surgical repair or at autopsies. Molecular tests have also been unsuccessful in demonstrating evidence of infection. The excellent response to steroids and immunosuppressive therapies (see below) also argues strongly against the aetiological role for infectious agents.

In recent years, the focus has shifted from infections to autoimmune processes. TA has been described in association with several immune system disorders such as ankylosing spondylitis, Still’s disease, Crohn’s disease, ulcerative colitis, interstitial lung disease, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune endocrine disorders, membranoproliferative glomerulonephritis, common variable immunodeficiency and Wiskott-Aldrich syndrome.

Inflammatory cell infiltration in the vessel wall points to involvement of cell-mediated immunity. CD4+ T cells are increased and CD8+ cells decreased in the circulation of TA patients, suggesting defective T cell regulation. Phenotypic analysis of infiltrating cells in aortic walls has shown a predominance of CD3+CD8+ cytolytic T lymphocytes. CD4+ T cells positive for γδ receptor constituted one-third of the cell infiltrating the aortic wall in TA but were virtually absent in atherosclerotic vessels. γδT cells play a pivotal role in cell-mediated cytotoxicity. Unlike αβT cells, they recognize small non-peptide antigens without the requirement of processing and presentation. γδT cells also recognize a family of proteins called heat shock proteins (HSP). The expression of one of these, HSP-65, has been shown to be markedly increased in the media of aortic tissue with TA. Patients with active disease also showed increased frequency of high tumour necrosis factor (TNF)-α and low interleukin (IL)-2 producing T cells. Increased perforin expression has been demonstrated in infiltrating cells. Upon release, perforins polymerize and assemble into transmembrane pores on the surface of arterial vascular cells and cause injury. A strong expression of Fas and Fas-ligand was also shown in the aortic vascular cells and infiltrating cells respectively. This pathway is important in induction of apoptosis. The failure to document apoptosis of aortic vascular cells, however, has cast a doubt on the significance of this finding.

Polymerase chain reaction analysis has shown overrepresentation of Vδ1+ T cells that recognize stress-inducible molecules MICA and MICB. Intercellular adhesion molecule-1 (ICAM-1) expression is increased in the *vasa vasora* of aortic tissue of TA patients. ICAM-1 is a ligand for lymphocyte function-associated antigen-1 (LFA-1) present on killer lymphocytes, and its up-regulation could represent increased T cell cytotoxic potential. Additional support for this mechanism is lent by finding of
increased expression of the B7 family of molecules that provide co-stimulatory signal for T cell activation. In toto, these findings suggest that an increased expression of MICA in the aortic tissue in genetically susceptible individuals may trigger infiltration by \( \delta 1 + \gamma \delta T \) cells. This along with HSP-65, leads to cytokine release and up-regulation of ICAM-1 and HLA expression.

The role of autoantibodies against aortic endothelial cells has been proposed in the pathogenesis of TA. Over 95% TA patients have circulating anti-aortic endothelial cell antibodies (AAECAs).\(^1\)\(^2\) In vitro studies showed that the expression of E-selectin and vascular cell adhesion molecule-1 and the production of interleukin (IL)-4, IL-6 and IL-8 increased after aortic endothelial cells were exposed to sera from TA patients.\(^1\)\(^3\), \(^1\)\(^4\) This was accompanied by increased apoptosis. However, AAECAs are also noted in other situations where vascular inflammation is prominent. Hence it is unclear whether the development of these antibodies precedes or follows the disease. Initial experiments showing induction of inflammatory aortitis in rabbits injected with aortic wall extracts could not be reproduced. The levels of cytokines such as monocyte chemoattractant protein (MCP)-1, RANTES (regulated on activation, normal T cell expressed and secreted), IL-12, IL-18 and IL-6 have been shown to be elevated in TA.\(^1\)\(^5\) Some correlate with disease activity. A role for matrix metalloproteinases (MMPs) has also been suggested.

\textit{Vasa vasorum}, a penetrating network of capillaries normally limited to the adventitia shows abnormalities in TA. Involved vessels exhibit a proliferation of this network, which reaches as deep as the intima. This allows passage to dendritic cells, macrophages, various T cell subsets, and natural killer cells deep into the vessel wall, where they can induce damage through release of cytokines, matrix metalloproteases, reactive oxygen intermediates and nitrosative stress, as well as production of perforin and recruitment of other cytotoxic cells.\(^1\)\(^0\), \(^1\)\(^6\) Some cytokines support the formation of granulomas. Local production of growth factors can induce myointimal hyperplasia and vascular occlusion. Vascular dilatation leading to aneurysm formation is an abnormal response to mural stress when destruction of elastica and media predominates over myointimal proliferation.

The proclivity of TA for young women prompted investigation of the role of sex hormones. Urinary oestrogen levels were found to be elevated in about 80% patients.\(^1\)\(^7\) Oestradiols promote leucocyte adhesion to endothelial cells, and may be involved in modulation of immune response of TA.

**Clinical features**

Clinical manifestations of TA are highly variable, and depend on the stage of disease and distribution of vascular lesions. The worldwide median peak disease onset is around 25 years of age. At one time it was thought that TA did not occur after the age of 40, but studies from the National Institutes of Health in the USA showed that 13% of patients were older than 40 years at diagnosis.\(^1\)\(^8\), \(^1\)\(^9\) About 17% were older than 40 in an Italian cohort.\(^2\)\(^0\) This condition has been recognized as late as the sixth and seventh decades.\(^1\) In older patients, the co-existence of atherosclerosis must be recognized. Some studies suggest that females predominantly show aortic arch involvement, whereas males have abdominal aortic disease.\(^2\)\(^1\)
The disease is classically described to run a triphasic course (Table 16.1). Phase I or the pre-pulseless phase is characterized by an inflammatory period dominated by non-specific systemic complaints. The next phase is the phase of vascular inflammation, and phase III refers to a burnt-out stage characterized by signs of arterial insufficiency. Most patients, however, do not show a sequential progression through the phases. Constitutional symptoms occur in 33% to 71% of patients and include muscle and joint pain (50%), feeling of ill health (33%) and fever (27%). In some series, as few as 16% patients had constitutional symptoms, and 10% were entirely asymptomatic. Hypertension is the presenting feature in 32% to 93%. Limb blood pressure (BP) readings may be inaccurate. Arm BP may be falsely low because of proximal stenoses, and measurements should be made in the lower limbs also. The only way to measure true systemic BP in those with extensive disease is by intra-arterial measurement, but is impractical for repeated measurements. Hypertension is most frequently caused by renal ischaemia secondary to stenosis of one or both renal arteries or suprarenal part of abdominal aorta. Alternative mechanisms include abnormal vascular compliance and baroreceptor dysfunction.

Considering the extent of vascular involvement in TA, a surprisingly small number of patients exhibit signs of vascular insufficiency. The chronic nature of the disease permits development of good collateral circulation that compensates for the effects of arterial insufficiency except in terminal vasculature like the renal arteries.

Autopsy studies show coronary arterial disease in about 10%. Clinical manifestations include angina, myocardial infarction and congestive cardiac failure. The pattern

| Table 16.1 Clinical features and laboratory findings in Takayasu arteritis |
|---------------------------------|---------------------------------|---------------------------------|
| Phase I                        | Phase II                        | Phase III                      |
| Pre-pulseless phase            | Phase of vascular inflammation  | Burnt-out phase                |
| Fever                          | Vessel pain and tenderness      | Claudications                  |
| Myalgias/arthralgias           | (Carotidynia)                   | Raynaud’s phenomenon           |
| Night sweats                   | Elevated ESR                   | Visual symptoms                |
| Weight loss                    | Hypergammaglobulinaemia         | Abdominal angina               |
| Fatigue/weakness               | Normocytic normochromic         | Angina pectoris                |
| Elevated ESR                   | Anaemia                         | Myocardial infarction          |
|                                | Leucocytosis                    | Cerebrovascular insufficiency  |
|                                |                                 | Absent/weak pulses             |
|                                |                                 | Hypertension                   |
|                                |                                 | Vascular bruits                |
|                                |                                 | Aortic regurgitation           |
|                                |                                 | Mitral regurgitation           |
|                                |                                 | Congestive cardiac failure     |
|                                |                                 | Pulmonary hypertension         |

ESR, erythrocyte sedimentation rate.
of abnormalities includes stenosis or occlusion of the proximal segments including the orifices, diffuse or focal arteritis, and coronary arterial aneurysms. Angiographic studies reveal pulmonary artery disease in about 70%.\textsuperscript{18} The lesions are mainly stenotic, and lack of aneurysmal lesions helps in differentiation from Behcet’s disease. Cardiopulmonary shunting may lead to angina in the absence of coronary arterial involvement. Carotid arterial involvement may lead to dizziness, syncope, transient ischaemic attacks or stroke. Seizures are seen only with hypertensive encephalopathy. Transient decrease in visual acuity may occur, especially with the head in extended position.

Retinal involvement could be a consequence of hypertension or a specific retinopathy of TA. The former is encountered twice as frequently as the Takayasu retinopathy.\textsuperscript{25} Initial features of TA are dilatation of small vessels and capillary microaneurysm formation, followed by vessel obliteration, arteriovenous shunt formation and neovascularization. Shunts can be seen at the AV crossings, around the papilla or as preferential circulatory channels.\textsuperscript{26} The occurrence of cataract, rubeosis iridis or glaucoma can result in blindness. Among the skin manifestations, erythema nodosum is more common in Caucasians, whereas pyoderma gangrenosum is predominantly seen in the Japanese. Rarely, glomerulonephritis (GN) has been associated with TA. A mild mesangial proliferation is the most frequent abnormality, but mesangiocapillary GN and amyloidosis have been recorded.

Differences are noted in the pattern of arterial involvement in different geographical regions. Aortic arch and its branches are predominantly involved in Japanese patients, whereas abdominal aortic disease is seen in a majority of Indian and Korean cases. The lesions are mostly stenotic in Japanese, American and European populations, whereas aneurysm formation is more commonly reported from India, Thailand and Mexico. Significant geographical variation is also noted in the frequency of major clinical features between different countries\textsuperscript{27} (Table 16.2).

**Table 16.2** Clinical features of Takayasu arteritis in different countries

<table>
<thead>
<tr>
<th>Parameter</th>
<th>USA</th>
<th>India</th>
<th>Japan</th>
<th>Mexico</th>
<th>Korea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claudication</td>
<td>70</td>
<td>23</td>
<td>13</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>43</td>
<td>2</td>
<td>27</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Myalgias/arthralgias</td>
<td>53</td>
<td>NS</td>
<td>NS</td>
<td>53</td>
<td>NS</td>
</tr>
<tr>
<td>Headache</td>
<td>42</td>
<td>30</td>
<td>30</td>
<td>57</td>
<td>31</td>
</tr>
<tr>
<td>Giddiness</td>
<td>35</td>
<td>18</td>
<td>40</td>
<td>NS</td>
<td>40</td>
</tr>
<tr>
<td>Weak/absent pulse</td>
<td>60</td>
<td>65</td>
<td>62</td>
<td>98</td>
<td>62</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33</td>
<td>43</td>
<td>33</td>
<td>76</td>
<td>33</td>
</tr>
<tr>
<td>Bruit</td>
<td>80</td>
<td>70</td>
<td>NS</td>
<td>94</td>
<td>NS</td>
</tr>
<tr>
<td>Asymmetric BP</td>
<td>47</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Carotodynia</td>
<td>32</td>
<td>9</td>
<td>21</td>
<td>NS</td>
<td>21</td>
</tr>
</tbody>
</table>

All figures are percentages
Data from \textsuperscript{5,18,48,69,70}.
BP, blood pressure; NS, not stated.
Pathology

On gross examination, the arterial involvement is patchy. Areas of thickening or thinning alternate with unaffected areas giving rise to focal stenoses or aneurysms. Involved vessels may manifest secondary atherosclerosis or luminal thrombi. Complete occlusion is rarely seen in abdominal aorta. Histology shows panarteritis. The adventitia and media show a mixed cellular infiltrate with giant cells and granuloma formation. The vasa vasora show endothelial proliferation and obliteration of their lumina. Intimal thickening as a result of mucopolysaccharide accumulation, degeneration of internal elastic lamina, smooth muscle proliferation and adventitial fibrosis are other findings. The rigid intima takes on a ‘tree bark’ appearance. The changes are similar to those seen in giant cell arteritis or aortitis associated with seronegative arthropathies. Skip lesions help in differentiation from syphilitic aortitis, which is diffuse and does not extend below the diaphragm.

Imaging studies

Conventional or digital subtraction angiography is the gold standard for imaging in TA. Abnormalities include irregularities in the wall and segmental stenosis of the aorta and its branches. The stenotic segments are usually long, smooth and exhibit tapered ends. Other findings include collateral vessels, aneurysms and total occlusions. The aneurysms may be saccular or fusiform in shape. A characteristic angiographic finding is patchy involvement: abnormal (stenotic or dilated) areas alternate with segments of uninvolved blood vessel (skip lesions). The 1994 International Takayasu Conference classified TA into five types based on angiographic appearance of the arterial tree (Table 16.3). Any of the types can be suffixed with C+ or P+ to indicate coronary or pulmonary arterial involvement. Over 50% of Indian and Japanese patients exhibit type V disease. Type IV disease is the next most common among Indians (28%), whereas types I and IIa predominate among the remaining Japanese patients (23%). In a study from Colombia, type I disease was the most common (34%), followed by types V (28%) and IV (20%). The exact frequency of pulmonary and coronary arterial involvement is not known as these systems are not imaged routinely. Renal arterial involvement is noted in over 60% of patients from India and Mexico.

Table 16.3 Angiographic classification of Takayasu arteritis

<table>
<thead>
<tr>
<th>Type</th>
<th>Site of involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Branches of aortic arch</td>
</tr>
<tr>
<td>IIa</td>
<td>Ascending aorta, aortic arch and its branches</td>
</tr>
<tr>
<td>IIb</td>
<td>Combination of type IIa and descending thoracic aorta</td>
</tr>
<tr>
<td>III</td>
<td>Descending thoracic aorta, abdominal aorta and/or renal arteries</td>
</tr>
<tr>
<td>IV</td>
<td>Abdominal aorta and/or renal arteries</td>
</tr>
<tr>
<td>V</td>
<td>Combination of types IIb and IV</td>
</tr>
</tbody>
</table>

Involvement of coronary arteries, C+; pulmonary arteries P+.
The major drawback of angiography is its inability to provide any information on the inflammatory status of the vessel wall. The invasive nature, risk of complications (albeit small), need of contrast use and cumulative radiation toxicity preclude its use to monitor disease progression.

**Ultrasonography (USG)**

Advances in technology, especially the advent of tissue harmonic imaging, Doppler studies and intravascular ultrasound, have extended the scope of USG in TA patients. USG can detect vessel wall thickening, luminal occlusion and dilatation and flow velocity alterations. Homogenous, circumferential thickening of intermediate echogenicity, especially when seen in young women, is highly specific for TA.\(^{31,32}\) Doppler USG can also be used to measure arterial stiffness. Stenotic lesions involving carotid and vertebral arteries can be identified with high sensitivity, and wall thickening can be appreciated even in the absence of any angiographic abnormality. In these locations, USG displays a resolution of 0.1–0.2 mm. Transcranial Doppler USG is useful in evaluating blood flow velocity and direction in large intracranial arteries.\(^{33}\) Evaluation of deep-seated vessels like pulmonary artery or abdominal aorta is difficult, but can be overcome to some extent with transoesophageal USG.

**Magnetic resonance imaging**

Magnetic resonance imaging (MRI) provides greater contrast between the different soft tissues of the body. Multi-planar MRI using both T1- and T2-weighted sequences in various planes, combined with gadolinium-enhanced 3D magnetic resonance angiography (MRA) permits delineation of vascular anatomy to a degree comparable with, if not better than, computerized tomography (CT) angiogram. Breath-hold contrast-enhanced 3D-MR angiography can achieve a sensitivity and specificity of 100%.\(^{34}\) Cine MRI helps in evaluation of functional and haemodynamic changes such as aortic regurgitation and pericardial effusions. Multi-sectional scanning by MRI allows better visualization of aortic and proximal pulmonary arterial walls.\(^{35}\)

In addition to identifying the location, degree and extent of luminal abnormalities and extent of collaterals, MRI has the added advantage of detecting altered signals within and surrounding inflamed vessels, which helps assessment of disease activity. In the acute phase, the aortic wall and surrounding adventitia enhance more than the myocardium. The delayed hyperenhancement in delayed gadolinium-enhanced MRI using specific inversion recovery prepared gated fast gradient-echo pulse sequence to null the signal from blood and the arterial wall, has been described as a specific finding. In one study,\(^{36}\) this finding correlated with C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR), thus suggesting that this technique could be used to assess disease activity and response to treatment.\(^{37}\) This needs to be examined in prospective studies. Its non-invasive nature and ability to depict systemic and pulmonary circulation without contrast use make it the preferred method for diagnosis and follow-up. In the late phase, MRI can provide a fast overview of aortic and pulmonary arterial anatomy from different imaging planes.
18F-fluorodeoxyglucose positron emission tomography

After injection into the bloodstream, the glucose analogue fluorodeoxyglucose (FDG) is taken up by cells in areas of high metabolic activity. FDG undergoes phosphorylation and gets trapped inside the cell. Labelling with a positron-emitting radionuclide (18F) permits its detection by positron emission tomography (PET). Abnormal FDG uptake is seen in the wall of inflamed vessels greater than 4 mm in diameter such as the aorta, its main branches or the pulmonary artery. 18F-FDG-PET scanning has the potential of non-invasively identifying inflamed vessels in TA not thought to be clinically active, thus allowing diagnosis in the pre-pulseless stage of the disease. It has been shown to be superior to MRI,38 and has the potential of being used as a monitoring tool.37,39 Several patterns of uptake have been described. In the early phase, the uptake is linear and continuous and becomes patchy as the activity subsides. In one study, 18F-FDG-PET was found to have a sensitivity and specificity of 92% and 100%, respectively, with a positive predictive value of 100% and a negative predictive value of 85%.40 The uptake comes down following immunomodulatory therapy, and correlates with changes in the acute phase responses such as ESR and CRP levels as well as disease activity scores.41 Use of PET in association with computerized tomography (PET-CT) permits a more accurate localization of 18F-FDG accumulation to the vessel wall in situations where PET alone fails to localize 18F-FDG accumulation.42

Diagnostic criteria

The non-specific nature of clinical manifestations, overlap with other conditions and lack of a pathognomonic test have prompted workers to put together a set of features that would permit a diagnosis with high degree of sensitivity and specificity. The most widely followed criteria were laid down by Ishikawa43 and consist of an obligatory criterion (age <40 years), two major criteria (lesions in left and right mid-subclavian arteries) and nine minor criteria including elevated ESR, carotid artery tenderness, hypertension, aortic regurgitation and lesions in pulmonary, left mid-common carotid, distal brachiocephalic arteries, and thoracic and abdominal aorta. Along with the obligatory criterion, presence of two major criteria or one major and two or more minor criteria suggest a high probability of TA. Ishikawa found a sensitivity of 84% in his 96 patients. A modified set of criteria (Table 16.4) allowed the diagnosis to be made with 92.5% and 96% sensitivity in Indian and Japanese patients respectively.44 Another set of criteria have been laid down by the American College of Rheumatology (Table 16.5). Presence of three or more criteria permitted diagnosis with a sensitivity of 90% and specificity of 98%.45

Assessment of disease activity and monitoring

It has been suggested that clinical monitoring aided by inflammatory markers should be used to assess disease activity, response to treatment and detection of relapse in TA.46 Persistence of active vascular inflammation has been shown on histology even when the disease is considered clinically quiescent or even ‘burnt out’. In one report, histology demonstrated active inflammation in the vessel walls among 44% of patients.
Table 16.4 Modified criteria for clinical diagnosis of Takayasu arteritis

<table>
<thead>
<tr>
<th>Major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Left mid-subclavian artery lesion: stenosis or occlusion 1 cm proximal to the left vertebral artery orifice up to 3 cm distal</td>
</tr>
<tr>
<td>2. Right mid-subclavian artery lesion: stenosis or occlusion from the right vertebral artery orifice to 3 cm beyond</td>
</tr>
<tr>
<td>3. Characteristic signs and symptoms (&gt;1 month duration)</td>
</tr>
<tr>
<td>A. Limb claudication</td>
</tr>
<tr>
<td>B. Pulselessness or blood pressure differential &gt;10 mmHg in arms</td>
</tr>
<tr>
<td>C. Exercise ischaemia</td>
</tr>
<tr>
<td>D. Neck pain</td>
</tr>
<tr>
<td>E. Fever</td>
</tr>
<tr>
<td>F. Amaurosis fugax</td>
</tr>
<tr>
<td>G. Syncope</td>
</tr>
<tr>
<td>H. Dyspnoea</td>
</tr>
<tr>
<td>I. Palpitations</td>
</tr>
<tr>
<td>J. Blurred vision</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. High ESR: Westergren ESR &gt;20 mm/hour</td>
</tr>
<tr>
<td>2. Carotodynia</td>
</tr>
<tr>
<td>3. Hypertension: brachial blood pressure &gt;140/90 mmHg of popliteal blood pressure &gt;160/90 mmHg</td>
</tr>
<tr>
<td>4. Aortic regurgitation or annuloaortic ectasia: determined by auscultation, arteriography or echocardiography</td>
</tr>
<tr>
<td>5. Pulmonary artery lesion: lobar or segmental artery occlusion, or stenosis or aneurysm of pulmonary trunk</td>
</tr>
<tr>
<td>6. Left middle common carotid artery lesion: stenosis or occlusion of middle 5 cm portion starting 2 cm from its orifice</td>
</tr>
<tr>
<td>7. Distal innominate artery lesion: stenosis or occlusion in the distal third</td>
</tr>
<tr>
<td>8. Descending thoracic aorta lesion: narrowing, aneurysm, or luminal irregularity</td>
</tr>
<tr>
<td>9. Abdominal aortic lesion: narrowing, aneurysm, or luminal irregularity</td>
</tr>
<tr>
<td>10. Coronary artery lesion: documented by arteriography in patients &lt;30 years of age and without risk factors for atherosclerosis</td>
</tr>
</tbody>
</table>

Two major, or one major and two minor, or four minor criteria indicate a high probability of Takayasu arteritis.

ESR, erythrocyte sedimentation rate.

thought to be in clinical remission.\textsuperscript{18} Active inflammation was present on autopsy in patients believed to be in the chronic, fibrotic phase of disease.\textsuperscript{28} Follow-up studies have shown that new lesions of TA develop even in the absence of clinical signs of activity. Obviously, doing biopsies to determine activity is impractical in TA, as the involved vessels are usually inaccessible.
TAKAYASU ARTERITIS

There are no reliable disease activity scores for TA akin to the Birmingham Vasculitis Activity Score (BVAS), a reliable indicator of disease activity for primary systemic vasculitis. Kerr et al. defined active TA as the new onset or worsening of two or more of the following features: fever or arthralgia; raised ESR (>20 mm/hour); features of vascular ischaemia or inflammation such as claudication, diminished or absent pulse, bruit, vascular pain, asymmetric BP in upper or lower limbs or typical angiographic features. New indices (DEI-TAK and ITAS) have been proposed using BVAS as a template. A number of potential ‘biomarkers’ have been proposed in the recent years. These include CRP, IL-6, 12 and 18, and matrix metalloproteases 2, 3 and 9. None of these, however, have been validated in large cohorts.

Management

The goal of management is identification of disease activity and amelioration of vascular inflammation in the early phases, and correction of ischaemia in the late occlusive phase. TA should be managed at a centre with adequate expertise in clinical assessment, imaging and vascular surgery. Glucocorticoids, either alone or in combination with alkylating agents have been the mainstay of treatment for patients with active inflammatory TA, defined traditionally by an elevated ESR. The initial therapy is usually with prednisone in a dose of 1 mg/kg/day (max. 60 mg/day). According to the European League Against Rheumatism (EULAR), the initial high dose should be maintained for 1 month and tapered gradually. Alternate day therapy is more likely to lead to a relapse, and is not recommended. At 3 months, the glucocorticoid dose should be 10–15 mg/day.

Table 16.5 American College of Rheumatology criteria for the diagnosis of Takayasu arteritis

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age at disease onset &lt;40 years</td>
</tr>
<tr>
<td>Development of symptoms or findings related to TA at age &lt;40 years</td>
</tr>
<tr>
<td>2. Claudication of extremities</td>
</tr>
<tr>
<td>Development and worsening of fatigue and discomfort in muscles of one or</td>
</tr>
<tr>
<td>more extremity while in use, especially the upper extremities</td>
</tr>
<tr>
<td>3. Decreased brachial artery pulse</td>
</tr>
<tr>
<td>Decreased pulsation of one or both brachial arteries</td>
</tr>
<tr>
<td>4. BP difference &gt;10 mmHg</td>
</tr>
<tr>
<td>Difference of &gt;10 mmHg in systolic BP between arms</td>
</tr>
<tr>
<td>5. Bruit over subclavian arteries or aorta</td>
</tr>
<tr>
<td>Bruit audible on auscultation over one or both subclavian arteries or</td>
</tr>
<tr>
<td>abdominal aorta</td>
</tr>
<tr>
<td>6. Arteriogram abnormality</td>
</tr>
<tr>
<td>Arteriographic narrowing or occlusion of the entire aorta, its primary</td>
</tr>
<tr>
<td>branches or large arteries in the proximal upper or lower extremities,</td>
</tr>
<tr>
<td>not due to arteriosclerosis, fibromuscular dysplasia or similar causes;</td>
</tr>
<tr>
<td>changes usually focal or segmental</td>
</tr>
</tbody>
</table>

For purposes of classification, a patient shall be said to have Takayasu arteritis if at least three of these six criteria are present.

BP, blood pressure.
Between 20% and 100% (mean 50%) respond; the median time to achieve remission can be as long as 2 years.\textsuperscript{47,48} As many as 50% patients relapse. Therefore, long and multiple treatment courses are necessary and long-term administration may be required to maintain therapeutic effect. It is still not known whether the ‘bone-sparing’ glucocorticoid, deflazacort, will be effective in TA.

The addition of cytotoxic drugs is required in steroid non-response patients or in those developing unacceptable side effects. In one study, immunosuppressive agent (methotrexate (MTX), azathioprine or cyclophosphamide) was added to steroids in 25 patients; eight achieved remission following addition of one agent and another four responded to a second agent. Rheumatologists prefer MTX because of their familiarity with this agent and the known toxic potential of cyclophosphamide. No controlled studies are available, however. In one open-label study, MTX, 0.3 mg/kg/week (not to exceed 15 mg/week), increased every 1–2 weeks to 25 mg/week was given with prednisone, to 16 steroid-resistant or -dependent patients. Over 80% achieved remission and maintained it over a 3-year period as defined by the absence of any clinical signs or new angiographic lesions.\textsuperscript{49} Regular monitoring of blood counts and liver enzymes is required to minimize toxicity. About 20% of patients fail to respond to steroids and alkylating agents.\textsuperscript{18}

Some novel treatment approaches are being tried in TA. They include the use of mycophenolate mofetil (MMF, an inhibitor of inosine monophosphate dehydrogenase), minocycline (an inhibitor of matrix metalloproteases) and anti-TNF\textsubscript{α} antibodies. In one study of 20 cases, a combination of steroids and MMF was able to induce remission in all, as evidenced by improvement in disease activity score and markers of inflammation. The authors were able to reduce the steroid dose by over 50%.\textsuperscript{50} In combination with steroids, minocycline induced clinical remission in nine out of 11 cases along with a decline in ESR and CRP.\textsuperscript{51} A recent treatment target is TNF\textsubscript{α}, an important inflammatory mediator. In one study,\textsuperscript{52} 15 steroid-dependent patients with multiple previous relapses received either infliximab (3 mg/kg to 5 mg/kg IV at weeks 0, 2, 6 and every 4–8 weeks thereafter) or etanercept (25 mg twice weekly). Ten achieved complete remission and in another four steroid dosage could be reduced by >50%. The response was maintained for 3.3 years. Other workers have shown similar results.\textsuperscript{53,54} In a case report, sildenafil was shown to be effective for amelioration of digital ischaemia in a child with TA who had failed therapy with steroids, infliximab, aspirin and heparin.\textsuperscript{55}

It has been suggested that prevention of myointimal proliferation could help arrest disease progression in TA. This could be achieved by drugs like statins and sirolimus (shown to be effective in cardiac allograft vasculopathy), or by targeted antagonism of growth factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor.\textsuperscript{56,57}

Although no compelling data are available, it seems prudent to recommend minimization of overall cardiovascular risk profile through control of blood pressure, dyslipidaemia, cessation of smoking and other lifestyle modifications. The use of low-dose aspirin and statins seems justified in view of their pleiotropic effects.

Hypertension, when mild or surgically uncorrectable, can be treated with pharmacological therapy. Angiotensin converting enzyme (ACE) inhibitors or angiotensin
receptor blockers are preferred in those with unilateral renal artery narrowing. Caution should be exercised in those with bilateral disease or suprarenal aortic stenosis because these drugs may worsen the ischaemia across the stenotic segment, precipitating renal failure. β-blockers should be avoided in patients with peripheral vascular disease. Pitfalls in measurement of blood pressure in limbs make management more difficult. Blood pressure should be measured in lower limbs in those with aortic arch or subclavian involvement.23

Revascularization

Indications for revascularization in TA include symptoms due to cervicocranial vessel stenosis, coronary artery disease, aortic regurgitation, severe coarctation of the aorta, renovascular hypertension, limb claudication, and in enlarging aneurysms with risk of rupture. The choice is between percutaneous revascularization with or without stent placement, and surgical bypass grafting. Any revascularization procedure should be delayed until active inflammatory disease has subsided.

Percutaneous transluminal angioplasty (PTA) aided by intravascular prosthetic devices (stents) has emerged as a powerful tool for management of stenotic lesions. In the beginning, it was thought that the lesions of TA may not be amenable to angioplasty because of their length and the ostial location. However, in recent years this technique has been used with increasing success in dilation of renal, carotid, subclavian, coronary and coeliac arteries and discrete lesions of the aorta. Careful selection of lesions for percutaneous procedures is important. PTA is most useful for management of renovascular hypertension because the lesions in the renal artery are usually short. In one study, technical success/improvement was achieved in 89% of renal arteries.58 Hypertension was cured in 65% patients and improved in another 20%. Blood pressure continued to be normal in 46% after a mean follow-up of 5.4 years. A fall in blood pressure is apparent within 24 hours and can continue for as long as 3 weeks, possibly due to a slow retraction of the fibrous strands and healing in a dilated state. In another study, restenosis developed in about 40% cases within 1 year. Self-expanding stents, both metallic and non-metallic, have been used as adjuncts to PTA.59,60 The latter have the advantage of not interfering with MRI that may be required for follow-up. Sirolimus-coated stents may be useful in preventing restenosis by interfering with neointimal hyperplasia.

Surgical bypass

Surgery is necessary in correction of long segment disease and when the lesions are not amenable to percutaneous procedure. Both synthetic graft (dacron or polytetrafluoroethylene) and autologous vessels (internal mammary artery or saphenous vein) have been used. The choice of material depends on the volume of flow that needs to be diverted. Synthetic grafts are required for large volume aortic lesions, whereas autologous vessels are reserved for branch or coronary artery lesion.61,62 Renal revascularization usually requires aortorenal bypass using synthetic grafts. The surgical technique is similar to that for any occlusive disease. Long-term patency depends on integrity of the anastomotic sites, and it is imperative that these be free of disease. This may require long grafts.
Endarterectomy has been recommended for limited ostial lesions in the splanchnic bed. Reinforcement of anastomotic suture line with a polytetrafluoroethylene patch can prevent development of anastomotic aneurysms. Surgical mortality in TA ranges from 5% to 20%. The use of systemic steroids in the peri-operative period has been suggested to minimize active inflammation. Factors that determine the outcome of surgery include presence or absence of disease activity, the choice of segment used for graft anastomosis and graft material. The risk of restenosis is higher when the disease is still active, the graft is placed at an inflamed area and when synthetic grafts rather than autologous vessels are used as conduit. On average, a 20% to 30% rate of restenosis or occlusion is reported on long-term follow-up. Equally important determinants are adequate preoperative evaluation and planning and availability of appropriate supportive care (e.g. mechanical ventilation and haemodialysis).

**Prognosis**

Difficulty in determining the time of onset makes interpretation of survival statistics somewhat unreliable. Ishikawa proposed a clinical classification of TA to indicate various prognostic groups (Table 16.6) in terms of the number of complications. Presence of more than one complication confers poor prognosis. In a study of 88 patients, overall survival at 5 and 20 years was 91% and 84% respectively. Event-free survival, defined by absence of stroke, heart failure, myocardial infarction, vision loss, renal failure, massive haemoptysis and haemorrhage, was 75% and 64% for the same duration. In another study, the 5-year survival was 94%. The major causes of death include congestive cardiac failure, cerebrovascular accident, myocardial infarction and renal failure. About three-quarters of patients experience some degree of morbidity with their disease, and 47% are estimated to acquire a permanent disability as a result of disease. Considering the young age of the affected population, the morbidity and mortality assumes significance.

**Juvenile TA**

TA is the third-most common vasculitis in childhood worldwide. Individuals under 20 years of age comprise 32–77% in large series of TA patients. The youngest reported case was diagnosed at 7 months. Systemic features (fever, headache, fatigue, myalgia, Table 16.6 Prognostic classification of Takayasu arteritis

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Uncomplicated disease with or without involvement of the pulmonary arteries</td>
</tr>
<tr>
<td>2</td>
<td>One complication*</td>
</tr>
<tr>
<td>2a</td>
<td>Mild to moderate disease with one complication</td>
</tr>
<tr>
<td>2b</td>
<td>Severe disease with one complication</td>
</tr>
<tr>
<td>3</td>
<td>Two or more complications</td>
</tr>
</tbody>
</table>

* Complications: retinopathy; secondary hypertension; aortic regurgitation; aortic or arterial aneurysm.
arthralgia, weight loss) are more common in paediatric TA patients, and often lead to misdiagnoses such as systemic lupus erythematosus or juvenile rheumatoid arthritis. Hypertension is noted in 50–93% cases, and may lead to congestive cardiac failure. Symptoms due to ischaemia are rare. Descending thoracic and abdominal aorta are the most frequent sites of involvement. Glucocorticoid therapy alone induces comparable levels of remission in paediatric patients, but the time to remission is usually shorter than in adults. Compared with adults, the mortality is three times higher in children with TA.

**TA and pregnancy**

TA has no effect on fertility, and pregnancy is more frequent in patients with TA than in those with other forms of vasculitis. Worsening of hypertension is noted in a majority with pre-existing hypertension. Pre-eclampsia and congestive heart failure develop in 20% and 4% respectively. Low birth weight is common and may be related to poor placental circulation due to maternal aortic disease. Poor prognostic indicators include worsening of hypertension, aneurysmal disease, extensive disease of abdominal aorta and renal vessels and cardiac failure. Therapeutic abortion may be necessary during the first trimester in high-risk patients. Vaginal route is the preferred method of delivery, and Caesarean section is needed only for obstetric indications. During labour, uterine contractions are associated with a surge in blood pressure, and shortening of second stage with a low forceps delivery may be required. In a review of all reported cases of pregnancy in TA, about 84% ended with delivery of a healthy child. The course of TA itself seems largely unaffected by pregnancy. In one study, however, 50% of patients showed improvement in inflammatory indices.

**Future directions**

Developments in understanding of angiogenesis promise to open up an entirely new treatment approach in patients with obliterative vascular disease such as TA. Factors that promote endothelial cell activation, migration and proliferation have been characterized. These include VEGF, acidic and basic fibroblastic growth factors (FGF), hepatocyte growth factor (HGF), insulin-like growth factor, platelet-derived growth factor, placental growth factor and transforming growth factor-β. An increase in circulating VEGF and HGF levels has been demonstrated at sites of tissue ischaemia, including in one case of TA. Recombinant VEGF, FGF and HGF have shown angiographically and histologically demonstrable increase in the number of collateral vessels in ischaemic limbs of experimental animals. Case reports have documented subjective and objective improvement in limb ischaemia in some patients. These proteins, however, have very short half-lives (3–5 minutes) and require repeated parenteral administration. Initial studies or arterial and intramuscular gene transfer in experimental animals and humans with atherosclerotic peripheral vascular disease and Buerger’s disease, have shown promising results in terms of protein expression and clinical improvement. Another exciting possibility is the use of stem cells to prevent or correct ischaemia. Some trials have shown initial promising results in various ischaemic conditions including coronary artery disease, stroke and peripheral vascular
disease. Although the possibility of providing a ‘biological bypass’ seems exciting, a number of issues remain to be resolved before this approach can enter fully fledged clinical trials. These include choice of appropriate formulation of growth factors(s), selection of suitable vector, route of administration and long-term risk of increase in incidence of cancers.

References

Papers of particular interest have been highlighted as:
  * of special interest
  ** of outstanding interest

   **An updated review of Takayasu arteritis in the young.

   ***An observational study showing that Takayasu’s arteritis is the main cause of renovascular hypertension in India.


   **Study showing the clear involvement of cells of immune system in the genesis of Takayasu’s arteritis.


   **Demonstration of the correlation between cytokines and disease activity in an observational study.


Chapter 17

Systemic sclerosis: Immunopathogenesis, clinical features, and treatment

Voon H. Ong and Christopher P. Denton

Introduction

Systemic sclerosis (scleroderma, SSc) is a chronic multi-system connective tissue disease of uncertain aetiology with an annual incidence of approximately 10 per million in the UK. With a peak age of onset between 30 and 50 years, SSc has a strong female predominance but the factors that are responsible for this are not apparent. The early hallmarks of SSc are autoimmunity and inflammation with widespread functional and structural microvasculopathy. In advanced disease, end-organ damage occurs as a result of progressive interstitial and vascular fibrosis in the skin and major internal organs.1 Two major subsets of scleroderma are recognized because of the major differences in the extent of skin involvement and the pattern of internal organ involvement: limited cutaneous systemic sclerosis (lcSSc) in which cutaneous involvement is limited to the hands, face, feet and forearms, and diffuse cutaneous systemic sclerosis (dcSSc) in which there is proximal extension of skin involvement above the elbows and knees and the trunk. A third subset describes a subgroup of patients who demonstrate involvement of the internal organs such as gastrointestinal system or lung fibrosis in the absence of skin disease and this subgroup, scleroderma sine scleroderma, will often present only when end-organ damage is clinically apparent. Although the outcome of SSc has improved considerably over the last decade, the disease carries the highest case fatality among the connective tissue diseases.2

Renal manifestations

Different types of acute and chronic renal involvement have been described in SSc. Most renal manifestations are clinically silent. Approximately half of asymptomatic patients may have clinical markers of renal involvement with proteinuria and increased creatinine. Occult renal pathology may be detected from autopsy studies in 60–80% of patients.3 The degree of severity varies from asymptomatic reduction in renal function to life-threatening involvement. The most severe of these is scleroderma renal crisis. In this regard, involvement of the kidney demonstrates the acute consequences of the microvasculopathy in SSc. In contrast to the slowly progressive vasculopathy in pulmonary arterial hypertension, the vascular changes in renal scleroderma develop
rapidly, perhaps due to the high levels of systemic blood pressure. The mechanisms driving the development of renal vascular lesions are distinct from those which lead to pulmonary vascular lesions. This may reflect the abnormal response to vascular injury resulting in differential levels of endothelial activation markers such as E-selectin in both renal and pulmonary vascular beds.4

**Scleroderma renal crisis (SRC)**

SRC affects 5–10% of all SSc patients, 10–15% of patients with dcSSc and very rarely 1–2% of patients with lcSSc and sine scleroderma.5,6 Historically, mortality among patients with SRC at 1 year was high, although early treatment with angiotensin converting enzyme (ACE) inhibitors has reduced this from 85% to 24%. During the period 1972–2002, the proportion of SSc-related deaths attributed to SRC decreased from 42% to 6%.7 Despite this improvement in short-term outcome, the long-term outcome for patients developing end-stage renal failure is poor and its mortality in SRC remains high. SRC therefore constitutes one of the few medical emergencies in rheumatology, requiring prompt diagnosis and early aggressive initiation of therapy to prevent morbidity and mortality.

**Clinical features**

First described in 1863, the cardinal features of SRC comprise a new onset of accelerated phase systemic hypertension greater than 150/85 obtained at least twice over a 24-hour period and a decrease in renal function by at least 30% in the calculated glomerular filtration rate (GFR). The blood pressure threshold of 150/85 is chosen because this level is defined by the New York Heart Association as significant hypertension. A repeat serum creatinine concentration and recalculation of the GFR should be obtained where possible to corroborate the initial results. The key features of SRC are shown in Table 17.1.

Specific symptoms of renal crisis may not be present at onset, although many will experience systemic symptoms of headaches, fever, malaise and exertional breathlessness. Features suggestive of end-organ damage include encephalopathy, hypertensive retinopathy associated with visual disturbances or generalized seizures. Some of these features such as seizures may occur in the absence of significant hypertension. Consequently, an alternative diagnosis of thrombotic thrombocytopenic purpura (TTP) is sometimes considered, but in the presence of scleroderma these clinical findings should suggest SRC until another diagnosis can be confirmed. Flash pulmonary oedema may occur, resulting from water and salt retention due to large overload and oliguria. Arrhythmias, myocarditis and pericarditis, if present, may indicate a poorer prognosis. These features will corroborate further the occurrence of SRC. Occasionally, these cardiac events may precede the crisis and high renin levels may lead to pulmonary congestion even in the absence of hypertension.

In up to a fifth of patients with SRC, the diagnosis of SSc is made at the time of the apparently primary accelerated hypertension.5 This emphasizes the need to carefully evaluate these patients for the presence of this disease, in particular in those who present with modest increase in blood pressures or creatinine. Confirmatory investigations
with nailfold capillaroscopy and autoimmune serology with anti-nuclear antibodies (ANA) and the hallmark SSc-associated autoantibodies may help to diagnose early scleroderma.\(^8\)

A related but distinct entity of acute renal impairment with thrombotic microangiopathy in the absence of malignant hypertension has been described. This is rare and constitutes approximately 11% of all SRC cases.\(^9\) It is important to appreciate that the blood pressure may be high for the individual patient and yet remain within the normal range. Other features of rapidly progressive renal impairment, thrombotic microangiopathy with thrombocytopaenia must be present to diagnose normotensive renal crisis. Normotensive renal crisis is thought to occur in those individuals who are on ACE inhibitors immediately prior to the onset of the crisis and may herald a worse prognosis compared with those who present with hypertension. The mechanism by which this occurs is not clear but it may be less dependent on the renin–angiotensin–aldosterone pathway activation and thus less responsive to ACE inhibitor. Other mediators of vascular endothelial activation such as endothelin-1 (ET-1) may be important in these cases. An alternative hypothesis is that the use of ACE inhibitors delays the presentation of the crisis, with ensuing chronic mild renal insufficiency leading up to the crisis.

### Laboratory parameters in SRC

Changes in haematological and clinical biochemistry indices may be observed in patients with SRC. Anaemia can be an early feature of renal crisis. Microangiopathic haemolytic anaemia and thrombocytopaenia are common and occur in up to 60% and 50% of cases, respectively, and occasionally, disseminated intravascular coagulation develops.\(^5\) Careful assessment of these laboratory abnormalities is critical to avoid
attributing these to immune-mediated consumption, as steroids may be indicated in idiopathic thrombocytopenia purpura, but are contraindicated in SRC. Other evidence of thrombotic microangiopathy includes elevated level of lactate dehydrogenase, low haptoglobin and presence of schistocytes in the peripheral blood smear. The severity of these abnormalities reflects the extent of microvascular aggregation of platelets. The serum LDH is elevated because of haemolysis and tissue damage from ischaemia. Increased serum creatinine may occur in over 96% of patients. Hyperreninaemia may be detected and this may be ameliorated with bilateral nephrectomy. Urinalysis commonly demonstrates a non-nephrotic range of proteinuria and microscopic haematuria with granular casts evident on microscopy.

An important but rare differential diagnosis that has been reported to co-exist with SSc is TTP. Like SRC, TTP is characterized by microvascular thrombi, mainly in small arteries and capillaries with rapidly progressive renal impairment, thrombocytopenia, microangiopathic haemolytic anaemia (MAHA) and neurological abnormalities. Hypertension, although it may occur in TTP, is not a typical feature and less likely to be as persistent as in SRC. The management of these two entities differ widely, so prompt recognition is important for appropriate treatment. In contrast to SRC, the pathophysiology of TTP depends on deficiency of von Willebrand factor (vWF) cleaving protease/ADAMTS13 (a disintegrant and metalloproteinase with a thrombospondin 1-like domain, member 13) that leads to accumulation of large vWF multimers. These multimers agglutinate circulating platelets and lead to the formation of microthrombi and presumably contribute to the atherogenesis of TTP. Assays for plasma ADAMTS13 activity can be a useful tool for differentiating these conditions from each other as these are very sensitive but not very specific tests.

Other forms of renal involvement in scleroderma

Indolent chronic renal involvement has been described in SSc, characterized by a slow reduction in glomerular filtration rate. Apart from SRC, other forms of acute renal complications may occur, especially in SSc overlap syndromes with other connective tissues diseases such as lupus nephritis. Serological clues may be present to suggest an evolving pattern of connective tissue disease spectrum, such as a rise in complements and emergence of anti-dsDNA antibody. It has been suggested that anti-neutrophil cytoplasm antibody (ANCA) reactivity may predict unusual renal complications of SSc, such as glomerulonephritis and renal vasculitis.

ANCA-associated vasculitis

Atypical ANCA antibodies have been reported in 20–30% of SSc patients, but this is usually clinically not significant. In contrast, there are only few case reports and case series on SSc patients with ANCA-associated systemic vasculitis in the current literature. In an unselected cohort of patients with SSc, approximately up to 7% of these patients may be positive for p-ANCA by immunofluorescence staining and the presence of both myeloperoxidase (MPO) and proteinase 3 (PR3) have been confirmed by enzyme-linked immunosorbent assay (ELISA). In our centre, of 2200 SSc patients, 1.6% had a current or previous history of vasculitis and distribution of the SSc-specific
autoantibody among these patients was broadly comparable with the entire SSc cohort. Approximately, a quarter of these patients were either anti-MPO or anti-PR3 antibody positive. In contrast to the patients with SRC, these patients tend to have lcSSc and may associate more with anti-MPO than with anti-PR3 antibody. Although a majority of the patients in our cohort develop glomerulonephritis, the clinical features were more heterogeneous than in either SSc or vasculitis alone. For example, none of the MPO-positive patients developed granulomatous diseases and a majority of patients had pulmonary fibrosis. Certain SSc antibodies such as anti-U3RNP antibodies may associate more with ANCA-associated vasculitis overlap syndrome than other SSc-specific antibodies. For example, no patients with vasculitis and anti-centromere antibodies in our cohort were ANCA positive. In contrast, other studies suggest that positive serology for Scl-70 was common in the ANCA-associated vasculitis. Therefore, the diagnosis of ANCA-associated vasculitis (AAV) in scleroderma overlap syndrome should be considered in any scleroderma patients with anti-MPO antibodies and renal failure. In addition, normotensive renal failure requires careful assessment of other aetiologies including vasculitis, especially when there is no evidence of MAHA or thrombocytopenia.

Isolated cases of crescentic glomerulonephritis and cases of pulmonary renal syndrome mimicking Goodpasture’s syndrome have also been reported with the use of penicillamine. In the latter, in contrast to typical findings of Goodpasture’s syndrome, there is notable absence of linear or granular deposition of immunoglobulin along the glomerular basement membrane. Penicillamine is now rarely used but, historically, it was used for treatment of skin disease in SSc.

**Anti-phospholipid antibodies and renal disease**

Although anti-phospholipid syndrome is rare in SSc, anti-phospholipid antibodies have been reported to occur in up to 63% of patients with SSc. It has been reported that both IgG anticardiolipin antibody and anti-β2 glycoprotein 1 antibodies correlated negatively with creatinine clearance as measured with Cockcroft-Gault and GFR as measured by the modification of diet in renal disease (MDRD) study equation. Proteinuria (>0.5 g/24 hours) was increased in those with anti-phospholipid (aPL) antibodies (21%) compared with those without aPL antibodies (9%). Similarly, renal crisis occurred in 21% of patients with aPL but not in patients without aPL. These preliminary observations are interesting but more detailed assessment is required to examine the role of these antibodies in SSc.

A similar association has been described between these antibodies and pulmonary hypertension suggesting that these pathogenic aPL may be relevant to the endothelial injury in both renal and pulmonary vasculature in SSc. aPL may bind to the phospholipids of the endothelial cells leading to reduction of prostacyclin release.

**Proteinuria in SSc**

Mild proteinuria without loss of renal function is the most common feature of SSc renal disease. A survey of 675 patients with dcSSc seen between 1972 and 1993 detected renal function abnormalities or proteinuria in 173 (26%) patients and 48% had no
demonstrable abnormalities. Most of the patients have a non-sclerodema-related cause of proteinuria including drug toxicity. Only 28 (4%) of these patients had an unknown cause for their renal dysfunction or proteinuria. Patients without evidence of renal crisis who have abnormal urinalysis, increased creatinine or proteinuria should be carefully investigated for non-scleroderma causes of renal disease.

It is well established that albuminuria is an important predictor of both cardiovascular and renal outcomes in chronic renal disease, and albuminuria has been postulated to reflect endothelial injury. Further studies are warranted to investigate the significance of proteinuria in SSc.

Isolated reduced GFR in SSc

Impairment in renal function may occur in the presence of normal serum creatinine in SSc and serum creatinine may remain normal until the GFR is less than 50% of normal limits. The relative contribution of tubular secretion of creatinine and extra-renal elimination of creatinine to the measured creatinine clearance increased with falling GFR, which exaggerates the discrepancy between creatinine clearance and measured GFR. For these reasons, serum creatinine measurements cannot be relied on to detect early renal involvement in SSc and the GFR remains the cornerstone for diagnosing renal disease.

Measurement of GFR is influenced by a variety of factors including structural and functional renal disease as well as patient’s age, weight and body surface area. The annual decline of GFR with age is approximately 1 ml/min/1.73 m² body surface area soon after the patient reaches an age between 20 and 30 years. The gold standard for GFR is inulin clearance but it is too costly and time-consuming for routine clinical practice. Other clearance methods have been developed for measurement of GFR and these include chromium-51-ethylenediaminetetraacetic acid clearance, technetium 99m diethylenetriamine-pentacetic acid or iohexol clearance. Using these techniques, measured GFR has been reported to be reduced in 10–55% of patients with SSc with serum creatinine within normal limits. Different inclusion criteria for renal involvement account for the wide range of figures quoted in the different case series. Although some of the renal impairment in these patients may be attributed to concomitant medical co-morbidities and D-penicillamine therapy, a significant proportion had unexplained renal insufficiency.

As an alternative to direct measurement of GFR, different formulae are available to calculate GFR as a means of screening of renal functional impairment. Of these formulae, the MDRD and Cockcroft-Gault formula have been widely used as indirect estimates of renal function. Measured GFR correlates well with calculated GFR when the MDRD equation is used and the MDRD formula may be more accurate in detection of reduced GFR in SSc patients with renal impairment than the Cockcroft-Gault Formula.

Current evidence suggests that functional renal impairment in SSc is mild to moderate and longitudinal series indicate that it often follows a benign non-progressive course. The reduced GFR appears to be independent of disease subset and other key clinical parameters including disease duration or disease severity. There is growing evidence
to indicate that the renal insufficiency may associate with pulmonary hypertension.\textsuperscript{23} It is plausible that the combination of SSc, pulmonary arterial hypertension and right heart failure may increase the probability of developing renal dysfunction with further fluid retention and neuroendocrine activation. This association may also suggest that both conditions may share similar aetiology with endothelial injury induced by various cytokines including ET-1, vascular endothelial growth factor and thrombomodulin leading to microangiopathy in the pulmonary and renal vascular beds.

**Impaired renal functional reserve**

A blunted renal functional reserve (RFR) has been described in SSc in the absence of clinically evident renal involvement. Renal haemodynamic and functional response to an amino acid load stimulates renal vasodilatation and hyperfiltration and the increase in GFR in response to such stimuli constitutes the RFR. Following an infusion of a standardized amino acid solution of Fremin III Baster, 8.5% solution, the increase in GFR was markedly reduced in SSc patients.\textsuperscript{24} This was associated with a lower effective renal plasma flow and increased calculated total renal vascular resistance.

A defective response in the endothelium-dependent vasodilatation is an integral feature of microvasculopathy in the early phase of SSc and, although the mechanism underlying the activation of the RFR is not fully understood, \textit{in vitro} studies indicate that the intrarenal regulatory balance between various vasoconstrictive and vasodilatory factors such as nitric oxide and angiotensin II may be relevant in RFR. Further studies are warranted to examine if the impaired RFR is predictive of significant renal disease.

**Pathogenesis of SRC**

The aetiopathogenesis of the renal events in SSc including SRC is incompletely understood (Fig. 17.1). The damage in SRC is likely to be a consequence of a chain of events to the kidneys culminating in thrombotic microangiopathy. The primary process in SRC is similar to the other widespread vasculopathy in other organs with an initial vascular endothelial injury. This will lead to a rapid increase in endothelial permeability and intimal oedema leading to intimal thickening. Subsequent to this key initial event, the subendothelial connective tissue is then in direct contact with the circulating blood elements including platelets. Consistent with the acute vascular injury in SRC, high levels of endothelial activation markers such as soluble adhesion molecules have been detected in sera from these patients irrespective of their cutaneous involvement. However, these markers were not consistently elevated at the time of SRC.\textsuperscript{4} Activation of the coagulation cascade and vascular thrombosis with release of various factors within the platelets may further aggravate the endothelial permeability and may favour the fibrotic microenvironment resulting in proliferative fibrovasculopathy (onion-skin lesion). The intimal proliferative changes predominantly affect the renal intralobular and arcuate arteries. Thrombotic microangiopathy is thought to be caused by excess fragmentation of red blood cells passing through these narrowed vessels and consumption of platelets. Decreased renal perfusion as a result of the arterial narrowing
leads to hyperplasia of the juxtaglomerular apparatus and excessive renin secretion, culminating in malignant hypertensive crisis and progressive renal injury. However, these vascular changes may occur even in patients with normal renal function and these abnormalities may reflect the vasculopathy that occurs pathologically in SSc. The presence of these changes appears to correlate with abnormal baseline renin response but they do not necessarily predict the development of SRC. Similarly, other kidney abnormalities such as proteinuria, hypertension and abnormal creatinine do not predict renal crisis. This may suggest that other factors other than hyperreninaemia may contribute to the crisis.

It is known that ET-1 contributes to the development and progression of chronic renal disease. Effects of ET-1 are mediated through ET_A and ET_B receptors, and several selective ET_A antagonists have been shown to improve renal blood flow and reduce renal vascular resistance.\footnote{25\textsuperscript{25}} There is a body of evidence to indicate that ET-1 is implicated in patients with SRC. Immunohistochemical studies demonstrated expression of ET-1 and ET_B receptors in renal biopsies at SRC.\footnote{26\textsuperscript{26}} ET-1 was overexpressed in the arteriolar lesions of mucoid arteriolar obstructions and intimal cellular proliferation.
and also within the glomerular lesions. Upregulation of ET\textsubscript{B} receptors was described in the vascular smooth muscles from the small renal arteries. Increased serum and plasma levels of ET-1 are detected in patients with hypertensive renal crisis.\textsuperscript{27} There is increased frequency in specific polymorphisms in the ET\textsubscript{B} genes among patients with dcSSc.\textsuperscript{28} These associations support a role of endothelin axis in the pathogenesis of SRC.

Tubulo-interstitial changes with tubular atrophy and interstitial fibrosis may be secondary to the vascular changes and this may be associated with a lymphocytic inflammatory infiltrate. Progression of the fibrotic response in SSc renal disease may reflect a final common pathway to different yet interlinked stages driven by TGF-\textbeta, the major fibrogenic cytokine, and myofibroblast transformation via epithelial to mesenchymal transition or endothelial to mesenchymal transition.

**Histology**

Macroscopically, gross changes of widespread petechial haemorrhages with areas of infarction and even cortical necrosis may be present on the surface of the affected kidneys, with wedge-shaped infarcts detected on cut sections of the kidneys. However, these observations are not specific to renal crisis and similar changes may be demonstrated in other thrombotic microangiopathic conditions such as TTP and idiopathic malignant hypertension or in association with some medications including anti-vascular endothelial growth factor therapy.

Microscopically, the biopsy reveals changes of thrombotic microangiopathy similar to those observed in other forms of malignant hypertension, but the thrombotic processes in SRC appear to affect the primary small vessels more than the glomerular apparatus. Microscopic changes are predominantly seen in the small interlobular and arcuate arteries (Figs 17.2 and 17.3). It is noteworthy that the pathological features may vary throughout the course of the SRC and the earliest vascular change is intimal oedema with accumulation of myxoid material composed of glycoprotein and mucopolysaccharide, and this is accompanied by proliferation of the intimal cells. Few lymphocytes or mononuclear cells are present. Fibrinoid necrosis is occasionally present either in arterial walls or in the subintimal layers but true vasculitis is only rarely observed (Fig. 17.4).

Subsequently, these pathological events will result in intimal thickening in the interlobular arteries, which in turn will lead to narrowing and, in some cases, obliteration of the vascular lumen with an onion-skin appearance. Adventitial and peri-adventitial fibrosis may be the only feature of chronic renal damage, but these are rarely noted in non-sclerodermatous malignant hypertension. Larger arteries, on the other hand, may be normal or demonstrate fibrous intimal thickening or atherosclerotic changes typical for the patient’s chronological age.

Acute glomerular changes may occur primarily or develop as a consequence of the vascular compromise and reduction in renal perfusion (Fig. 17.5). Electron microscopic evaluation may detect endothelial swelling and accumulation of glomerular subendothelial electron lucent material that may occur as a consequence of primary glomerular injury. In addition, glomerular capillary thrombosis may be present but
Fig. 17.2  Proliferative vasculopathy affecting interlobular vessel (stained with CD34 as endothelial marker) with complete luminal obliteration.

Fig. 17.3  Thrombotic microangiopathy in scleroderma renal crisis. Thrombotic occlusion of small arteries is shown.
Fig. 17.4 Fibrinoid necrosis is seen to affect the arterial wall with obliteration of the lumen.

Fig. 17.5 Renal biopsy of scleroderma renal crisis histology. Secondary glomerular ischaemia with tuft retraction (smooth muscle actin staining ×10).
these changes are fairly infrequent. Secondary glomerular changes may lead to ischaemic collapse of capillary loops. Hypertrophy of the juxtaglomerular apparatus may occur as a consequence of the hyperreninaemic state with severe arterial narrowing in SRC. Tubules are also secondarily affected by the vascular insufficiency from arterial luminal occlusion. This is manifest as acute tubular injury and may ultimately be replaced by flattening and atrophy of the tubular cells and interstitial fibrosis.

In the advanced stages of SRC, it may be difficult to distinguish chronic vascular changes associated with SRC from chronic accelerated essential hypertension.

Immunofluorescence microscopy identifies immunoglobulin deposits, predominantly immunoglobulin (Ig)M subclass with complement deposits in the glomeruli and blood vessels. Presence of granular C4d as a complement split product may be detected in the peri-tubular capillaries in SRC. These findings, however, are not diagnostic of SRC and may be attributed to gross disruption of vascular integrity and increased vessel permeability rather than immune injury. Immunofluorescent microscopy and electron microscopy are therefore not routinely utilized unless there is a clinical suspicion of overlap syndrome such as systemic lupus erythematosus (SLE) or vasculitis.

**Risk factors for SRC**

The development of SRC appears to be associated with dcSSc, accounting for approximately 65–85% of cases. However, only a minority of patients with dcSSc will develop SRC. It would therefore be helpful to identify risk factors that may predict development of this complication. Risk factors for renal crisis are listed in Table 17.2.

Patients with early dcSSc are at greatest risk: with the estimated median disease duration from the onset of non-Raynaud’s symptom to the initial presentation of renal crisis being only 8 months.5 Approximately two-thirds of SRC cases occur within a year of diagnosis of SSC, and up to 86% of SRC have been reported to occur within the first 4 years of disease. Rapidly progressive skin disease and tendon friction rubs in dcSSc represent other independent risk factors. In contrast, patients with lcSSc typically develop SRC later in the SSC disease course.

Evidence from retrospective studies and a recent review of prospective studies support the observation that SRC is associated with the use of corticosteroids, and 50–60% of patients received corticosteroids prior to the acute hypertensive crisis.

<table>
<thead>
<tr>
<th>Table 17.2 Risk factors for scleroderma renal crisis</th>
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<tbody>
<tr>
<td><strong>Early onset diffuse cutaneous systemic sclerosis</strong></td>
</tr>
<tr>
<td>Active progressive skin disease</td>
</tr>
<tr>
<td>Presence of tendon friction rubs</td>
</tr>
<tr>
<td>Recent high-dose steroid use</td>
</tr>
<tr>
<td>Anti-RNA polymerase III antibody</td>
</tr>
<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>New onset cardiac failure</td>
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A recent history of high-dose corticosteroid use (e.g. prednisolone or equivalent at >15 mg/day) may precede SRC diagnosis. The odds ratios for developing SRC associated with steroid therapy during the preceding 1- or 3-month periods were approximately 24 and 17 respectively.6

Although chronic corticosteroid use may not be associated with additional risks, a greater number of patients who had recently commenced on low-dose corticosteroids developed SRC versus controls. The risk is further increased in some cases of early dcSSc during which steroid therapy is likely to be used. This is highlighted by an increased number of cases of SRC reported in patients who have undergone autologous or allogeneic haematopoietic cell transplantation for severe SSc disease.29 Although there is no evidence of a causal effect, extreme caution is necessary when using high or medium doses of corticosteroid in dcSSc. Steroid usage should be restricted to patients with progressive lung fibrosis, inflammatory myositis, arthritis and tenosynovitis and the early inflammatory phase of active skin disease.

Other risk factors for SRC include anaemia, hormone replacement therapy, pericardial effusion, cardiac insufficiency, high skin score and large joint contractures and new cardiac events.30 Most of these may reflect the severity of the disease without a plausible causative role in the aetiopathogenesis of renal crisis.

A majority of patients with SSc harbour ANAs, and a strong association is observed between SRC and an ANA speckled pattern (with or without a nucleolar pattern but rarely nucleolar alone), which occurs in about two-thirds of the SRC patients.5 The incidence of renal disease is also significantly higher in patients with antibodies targeting RNA polymerase III (often together with RNA polymerase I, or I and II). These antibodies represent an important subgroup of anti-nucleolar antibodies defined by their characteristic appearance on indirect immunofluorescence on cells from a variety of species, although this pattern is not always observed with many anti-RNA polymerase antibody-positive sera. Commercial anti-RNA polymerase antibodies III (ARA) ELISA methods are now available, which makes identification of these antibodies simpler.

These antibodies are strongly associated with dcSSc, with 67–93% of ARA-positive subjects reported to have this subset.31 Most studies support that the presence of ARA is strongly predictive of SRC, with up to 43% of ARA positive subjects developing this internal organ complication; in addition, up to 59% of patients with SRC have been reported to be positive for ARA.32,33 The marked geographical variation in prevalence of ARA positivity (4–25%) in SSc may account for the differences in the prevalence of ARA positive patients developing SRC in some studies.34 Absolute ARA levels do not predict organ complications or disease outcome, although ARA positive patients appear to develop SRC earlier in their disease course compared with other autoantibody subgroups of patients.32

Other members of anti-nucleolar antibodies including anti-fibrillarin or anti-U3-RNP and anti-Pm-Scl antibodies may also identify another subset of patients at risk of developing internal organ complications of SSc including SRC.35 In contrast, SSc patients harbouring anti-centromere antibody or anti-topoisomerase I antibody are less likely to develop SRC compared with other SSc-specific antibodies.5,31

Association studies of HLA genetic markers with SRC in a large North American SSc registry recently identified HLA-DRB1*0407 (OR 3.21) and DRB1*1304 (OR 4.51) as
independent risk factors for SRC. Patients with these HLA genotypes have odds ratios of developing SRC similar to the presence of ARA. However, in contrast to other HLA genotypes, the predictive significance of DRB1*0407 and *1304 appear to be independent of autoantibody status. Further confirmation of these results in an independent cohort is required.

Identification of those at greatest risk has significant implications on management of these patients. A detailed risk assessment of patients with newly diagnosed SSc may facilitate early detection of the warning symptoms and signs of SRC. In those individuals with the aforementioned risk factors, regular monitoring of blood pressure on a monthly basis with daily self-monitoring is introduced if features of increased blood pressure developed.

A brief outline of these measures on a patient information leaflet with an appropriate contact for medical assistance will be invaluable. If appropriate, further assessment with quantification of serum creatinine concentrations and evaluation of protein content and protein-to-creatinine ratios in urine may assist in early detection of suspected SRC cases.

**Outcome and prognosis of SRC**

Despite the improvement in mortality with ACE inhibitors, the outcome of renal involvement in SSc remains a major concern with high mortality of approximately 30% at 3 years and 50% at 10 years from multiple causes. Overall, approximately 25% of patients with SRC will require dialysis at initial presentation, sufficient renal function will recover in most patients for them to discontinue dialysis. However, up to two-thirds of these patients may never regain renal function and will require permanent renal replacement therapy or transplantation. Long-term survival in this group of patients is poor (Fig. 17.6). Ultimately, it would be desirable to be able to stratify patients with SRC and to selectively identify those who are likely to require renal replacement therapy.

The median time to renal recovery allowing discontinuation of dialysis is approximately a year, with renal recovery after 24 months uncommon and rare after 3 years. Among those who do not require dialysis at initial presentation, there is a gradual improvement in eGFR for at least 3 years, reflecting a slow recovery process possibly associated with vascular remodelling.

Predictors of poor renal outcome include low blood pressure at initial presentation, older age if dialysis is required, high skin score above 20 and evidence of cardiac involvement (Fig. 17.7). Steroid use prior to onset of SRC was reported in up to 60% of SRC but it is not associated with poor renal outcome. Presence of MAHA may be associated with more severe hypertension and a higher frequency of renal dysfunction, but this observation is not consistent across all studies.

Although renal biopsy may not be absolutely necessary for the diagnosis of SRC in the presence of appropriate clinical features, it may facilitate prognostication of the patient outcome.

The severity and extent of acute vascular changes with myxoid intimal thickening, fibrinoid changes and thrombosis is predictive of poor outcome with half of these patients requiring permanent renal replacement therapy compared with 13% of those without.
Secondary glomerular ischaemic collapse and acute tubular necrosis may also be associated with poor prognosis. In contrast, chronic pathological changes with high index score did not correlate with poor outcome.

Large-scale studies from different countries have demonstrated that renal involvement is an important independent adverse predictor for mortality, in particular in those with pulmonary hypertension. Presence of proteinuria as detected on urine dipstick analysis is independently associated with increased mortality.\textsuperscript{37,38} The reasons for this

**Fig. 17.6** Survival following scleroderma renal crisis by renal outcome. Patients who required permanent dialysis had the poorest survival of all three groups of renal outcomes. With permission.\textsuperscript{5}

**Fig. 17.7** Effect of presenting diastolic blood pressure on renal outcome in scleroderma renal crisis (mean, 95% CI). Higher blood pressure at presentation is associated with a better outcome. With permission.\textsuperscript{5}
observation are not clear but it is likely that proteinuria may be a surrogate marker of endothelial activation.

**Treatment of SRC**

Aggressive treatment of hypertension in SRC patients is critical in preventing the occurrence of end-stage vascular injury. In all cases, hospitalization and prompt initiation of ACE inhibitors is essential and would dramatically improve blood pressure in a majority of patients. The role of ACE inhibitors in the treatment of SRC is to admit all cases at diagnosis and treat with full-dose ACE inhibitors. Currently, our approach to SRC is to admit all cases at diagnosis and treat with full-dose ACE inhibitors. Randomized controlled trials evaluating the efficacy of ACE inhibitors in the treatment of SRC are lacking and the current published evidence from numerous case series and uncontrolled studies includes mainly captopril and enalapril. There was no clear difference in the outcome of patients treated with either ACE inhibitor. Captopril, however, has a shorter half-life and it may allow flexibility and close titration of blood pressure. There is the potential risk of rebound hypertension, especially if the dose is inadvertently omitted in the acute crisis. The dose should be increased daily to achieve a blood pressure reduction of 10–20 mm Hg systolic/24 hours, and to avoid any prolonged periods of hypotension. An excessive reduction in blood pressure may further compromise renal perfusion and increase the risk of acute tubular necrosis. Once the blood pressure has stabilized, it may be replaced with a longer-acting ACE inhibitor. It is not unexpected that there may be continued deterioration in renal function, which can be monitored with daily creatinine clearance or calculated GFR.

Patients are routinely given continuous low-dose prostacyclin, which may help in normalization of blood pressure and has potentially beneficial effects on renal blood flow, endothelial cell function and production of proinflammatory or profibrotic factors. Although this is currently without formal confirmation of benefit, a continuous regime of intravenous prostacyclin is routinely used in some centres to manage the acute hypertensive crisis and this is then gradually weaned off once the renal function improves or at the initiation of renal replacement therapy. There is little evidence to support the choice of peritoneal dialysis over haemodialysis.

If the blood pressure is not adequately controlled, additional anti-hypertensive agents may be useful including combinations of angiotensin receptor blockers and ACE inhibitors or calcium channel blockers, nitrates (especially if pulmonary oedema) or other vasodilator agents such as doxazosin. Care must be taken to monitor cardiac function closely. Vasodilatation may be associated with relative hypovolaemia. Systemic vascular resistance monitoring using an oesophageal Doppler probe can be used and offers an alternative to more invasive monitoring such as pulmonary arterial balloon catheter. Plasma exchange has been reported to be useful in severe MAHA. All cases in our unit have renal biopsy. This may provide prognostic information and also confirms the diagnosis. A number of cases of SSc with inflammatory glomerular pathology have been identified and these require potentially very different treatment to classical SRC. The management of renal crisis in SSc is summarized schematically in Fig. 17.8.
Although treatment has improved over the last few decades, the outcome of SRC remains inadequate. Early mortality approaches 10% and up to half of patients need dialysis. This may be temporary, with up to half of the cases needing renal replacement therapy eventually coming off dialysis, although this may be between 6 and 24 months after the initial SRC. Renal transplantation should therefore not be made until at least 2 years after SRC. Renal allograft survival rates appear to be similar to survival rates for SLE. Although graft survival is poorer compared with the general transplant population, patient survival was significantly prolonged in those who received transplants compared with those who remained on the transplant waiting list. There is some evidence that transplantation may ameliorate the systemic features of the SSc such as skin activity, but this may be related to the immunosuppressive therapy used in kidney transplantation. Although recurrence of SRC with thrombotic microangiopathy has been reported in some cases, this remains rare.

Fig. 17.8 Algorithm for management of scleroderma renal crisis. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; MAHA, microangiopathic haemolytic anaemia; SSc, scleroderma.

Prevention of renal disease

There is no evidence to suggest that preventive measures are efficacious in decreasing the rates of SRC. However, patients who are at clinical risk of developing SRC are advised to recognize symptoms of accelerated hypertension and to monitor blood pressure regularly, in particular in the first 4 years of their disease. Similar approaches are also given to the physicians looking after these patients to ensure prompt diagnosis of SRC and to facilitate timely medical intervention. In addition, high doses of steroid and nephrotoxic drugs such as cyclosporine should be avoided. Steroids may be
required to treat specific complications associated with SSc such as lung fibrosis or inflammatory myositis. Under these circumstances, close monitoring of blood pressure is imperative.

Some experts have advocated the use of prophylactic ACE inhibitors even in the absence of Raynaud’s or hypertension. However, recent evidence suggests that the long-acting ACE inhibitor, quinapril, is not effective in SSc-associated vasculopathy including Raynaud’s phenomenon. Importantly, recent retrospective data in patients with SRC suggested that patients on ACE inhibitors prior to the onset of SRC may have a worse renal outcome than those not taking these drugs. It has been postulated that these patients may have developed normotensive renal crisis and the use of ACE inhibitors may have delayed the diagnosis of SRC. Most centres would advise that unless the patients have underlying hypertension, routine use of ACE inhibitors in SSc should not be recommended.

Conclusion

The introduction of ACE inhibitors over the last few decades has led to significant improvement in overall survival in SSc. However, SRC remains an important complication of this disease and there is still a high morbidity and mortality in scleroderma patients who develop acute hypertensive crisis. SRC is characterized by malignant hypertension, hyperreninaemic state, thrombotic microangiopathy and renal impairment. Risk factors may identify those who are at increased risk of developing SRC, and both physicians and patients should be vigilant to monitor for early warning signs and symptoms of the crisis to ensure early diagnosis and timely intervention. The recently made available assay for ARA should help to improve the risk stratification of renal crisis in early stage disease. International collaboration in future research is necessary to investigate surrogate markers such as vWF and ET-1 as prognostic indicators and potential targets for therapy for renal disease. Novel therapeutic agents used in other manifestations of vasculopathy in scleroderma and related connective tissue diseases may be explored as potential treatments in scleroderma renal disease.

References

REFERENCES


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Introduction

Amyloidosis is a disorder of protein folding in which normally soluble plasma proteins are deposited in the extracellular space in an abnormal insoluble fibrillar form. Accumulation of these fibrils causes progressive disruption of the structure and function of any body tissue or organ. Without treatment systemic disease is usually fatal, but measures that reduce the supply of amyloid fibril precursor proteins can frequently lead to regression of amyloid deposits, prevention of organ failure and improved survival. However, as the regression of amyloid is relatively slow, early diagnosis greatly improves the prognosis. Amyloid is remarkably diverse and can be hereditary or acquired, localized or systemic, and lethal or merely an incidental finding. It is rare but not especially so, with systemic amyloidosis being responsible for about one in 1500 deaths in the UK.

Amyloid structure

Amyloid deposits consist mainly of protein fibrils, the different peptide subunits of which provide the basis for its classification (Table 18.1). Despite the diversity of the various amyloid fibril precursor proteins, all amyloid deposits share a common structure and contain universal non-fibrillar elements, notably including heparan sulphate proteoglycans, apolipoprotein-E and the normal plasma glycoprotein, serum amyloid P component (SAP).

Although it is not clear why only the 29 or so known amyloidogenic proteins form amyloid in vivo, relative instability of the fibril precursor proteins is a common theme. Even under physiological conditions they populate partly unfolded states, involving loss of higher order structure and retention of β sheet secondary structure, which readily auto-aggregate into protofilaments and mature fibrils. Once the process has started, amyloid deposition may progress very rapidly, the template of amyloid in the tissues effectively capturing further like molecules. The ultrastructural morphology and histochemical properties of all amyloid fibrils, regardless of protein type, are remarkably similar, the electron microscope demonstrating straight, non-branching fibres of 10–15 nm in diameter. They are insoluble in vivo, relatively resistant to proteolysis, and bind Congo red dye in a spatially organized fashion that produces pathognomonic red-green birefringence under cross-polarized light. X-ray diffraction patterns demonstrate
### Table 18.1 Classification of amyloidosis

<table>
<thead>
<tr>
<th>Type</th>
<th>Fibril protein precursor</th>
<th>Clinical syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>Serum amyloid A protein</td>
<td>Reactive systemic amyloidosis associated with acquired or hereditary chronic inflammatory diseases</td>
</tr>
<tr>
<td>AL</td>
<td>Monoclonal immunoglobulin light chains</td>
<td>Systemic amyloidosis associated with myeloma, monoclonal gammopathy, occult B cell dyscrasia</td>
</tr>
<tr>
<td>AH</td>
<td>Monoclonal immunoglobulin heavy chains</td>
<td>Systemic amyloidosis associated with myeloma, monoclonal gammopathy, occult B cell dyscrasia</td>
</tr>
<tr>
<td>ATTR</td>
<td>Normal plasma transthyretin</td>
<td>Senile systemic amyloidosis with prominent cardiac involvement</td>
</tr>
<tr>
<td>ATTR</td>
<td>Genetically variant transthyretin</td>
<td>Familial amyloid polyneuropathy, usually with systemic amyloidosis. Sometimes prominent amyloid cardiomyopathy or nephropathy</td>
</tr>
<tr>
<td>Aβ2M</td>
<td>β2-microglobulin</td>
<td>Peri-articular and, occasionally, systemic amyloidosis associated with renal failure and long-term dialysis</td>
</tr>
<tr>
<td>AAPoAl</td>
<td>Apolipoprotein Al</td>
<td>Autosomal dominant systemic amyloidosis. Predominantly non-neuropathic with prominent visceral involvement</td>
</tr>
<tr>
<td>AAPoAll</td>
<td>Apolipoprotein All</td>
<td>Autosomal dominant systemic amyloidosis. Predominantly non-neuropathic with prominent visceral involvement</td>
</tr>
<tr>
<td>AAPoAlIV</td>
<td>Apolipoprotein Al</td>
<td>Senile systemic amyloidosis</td>
</tr>
<tr>
<td>AFib</td>
<td>Fibrinogen α-chain</td>
<td>Autosomal dominant systemic amyloidosis. Non-neuropathic with prominent visceral involvement</td>
</tr>
<tr>
<td>ALys</td>
<td>Lysozyme</td>
<td>Autosomal dominant systemic amyloidosis. Non-neuropathic with prominent visceral involvement</td>
</tr>
<tr>
<td>ACys</td>
<td>Cystatin C</td>
<td>Hereditary cerebral haemorrhage with cerebral and systemic amyloidosis</td>
</tr>
<tr>
<td>AGel</td>
<td>Gelsolin</td>
<td>Autosomal dominant systemic amyloidosis. Predominant cranial nerve involvement with lattice corneal dystrophy</td>
</tr>
<tr>
<td>ALECT2</td>
<td>Leucocyte chemotactic factor 2</td>
<td>Systemic amyloidosis with predominant renal involvement. Apparently sporadic</td>
</tr>
<tr>
<td>AIAPP</td>
<td>Islet amyloid polypeptide</td>
<td>Amyloid in islets of Langerhans in type II diabetes mellitus and insulinoma</td>
</tr>
<tr>
<td>Aβ</td>
<td>β-protein precursor (and rare genetic variants)</td>
<td>Cerebrovascular and intracerebral plaque amyloid in Alzheimer’s disease. Occasional familial cases</td>
</tr>
<tr>
<td>ABr</td>
<td>ABrPP</td>
<td>Hereditary dementia, British</td>
</tr>
<tr>
<td>ADan</td>
<td>ADanPP</td>
<td>Hereditary dementia, Danish</td>
</tr>
<tr>
<td>AprP</td>
<td>Prion protein</td>
<td>Spongiform encephalopathy</td>
</tr>
<tr>
<td>ACal</td>
<td>Procalcitonin</td>
<td>Amyloid associated with C cell thyroid cancer</td>
</tr>
<tr>
<td>AANF</td>
<td>Atrial natriuretic peptide</td>
<td>Cardiac atrial amyloid</td>
</tr>
</tbody>
</table>
a common core structure within the filaments, in which the subunit proteins are arranged as a stack of twisted anti parallel $\beta$ pleated sheets lying with their long axes perpendicular to the fibril axis. In some instances the fibrils in vivo are composed of intact whole precursor molecules, for example in lysozyme and $\beta_2$-microglobulin amyloidosis, but more often, the precursor proteins undergo partial cleavage, although it is not known whether this occurs before, during or even after fibril formation.

In clinical practice amyloid deposition occurs in three different circumstances. First, when there is abnormal abundance of a structurally normal precursor protein, such as in the cases of dialysis related amyloid in which the precursor is $\beta_2$-microglobulin, and in AA type in which the precursor is the acute phase reactant serum amyloid A protein (SAA). The second situation arises when a normal but intrinsically amyloidogenic protein has been present in normal quantities for a very prolonged period. An example of this is senile cardiac amyloidosis in which wild-type transthyretin accumulates as amyloid in the myocardium of elderly individuals. The third and most common situation with respect to systemic amyloidosis, is amyloid deposition involving a protein with an abnormal inherently amyloidogenic structure. Examples of this include acquired monoclonal immunoglobulin light-chain (AL) amyloidosis in patients with clonal plasma cell dyscrasias, and the autosomal dominant hereditary amyloidosis syndromes associated with genetically variant forms of transthyretin, fibrinogen A $\alpha$-chain, lysozyme, apolipoprotein A1, apolipoprotein A2, cystatin C and geloslin.

Although amyloid fibrils can be produced in vitro from their respective precursor proteins alone, there is evidence that the minor non-fibrillar elements that are found in all amyloid deposits contribute to the process in vivo. The significance of glycosaminoglycans (GAGs) in amyloid remains unclear, but their universal presence, intimate relationship with the fibrils and restricted heterogeneity all suggest that they play important roles in amyloidogenesis. Furthermore, low molecular weight polysulphonated compounds that are thought to act in vivo as ‘GAG-mimetics’, by preventing the association of amyloid fibrils with endogenous GAGs, inhibit experimental induction of AA amyloid deposits in mice and have been developed for use in man.

<table>
<thead>
<tr>
<th>Type</th>
<th>Fibril protein precursor</th>
<th>Clinical syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>APro</td>
<td>Prolactin</td>
<td>Prolactinoma</td>
</tr>
<tr>
<td>AMed</td>
<td>Lactadherin</td>
<td>Senile aortic media</td>
</tr>
<tr>
<td>AIns</td>
<td>Insulin</td>
<td>Iatrogenic amyloid deposits at injection site</td>
</tr>
<tr>
<td>AKer</td>
<td>Keratoepithelin</td>
<td>Hereditary corneal dystrophies</td>
</tr>
<tr>
<td>ALac</td>
<td>Lactoferrin</td>
<td>Corneal amyloidosis</td>
</tr>
<tr>
<td>AOaap</td>
<td>Odontogenic ameloblast associated protein</td>
<td>Odontogenic tumour-associated amyloid</td>
</tr>
<tr>
<td>ASeml</td>
<td>Semenogline I</td>
<td>Seminal vesicle amyloid</td>
</tr>
<tr>
<td>ATau</td>
<td>Tau protein</td>
<td>Alzheimer’s disease, fronto-temporal dementia</td>
</tr>
<tr>
<td>AGal</td>
<td>Galectin-7</td>
<td>Localized cutaneous macular and lichen amyloidosis</td>
</tr>
</tbody>
</table>
non fibrillar constituent that is present in relative abundance in all amyloid deposits is the plasma glycoprotein SAP component.\textsuperscript{7} SAP has close structural homology with C-reactive protein (CRP), the classical acute phase reactant, and they are members of the pentraxin family of plasma proteins. SAP and CRP are disc-like pentamers composed of identical non-covalently associated protomers, each of which has a calcium-dependent ligand binding site. In the case of SAP this enables it to bind to an as yet uncharacterized ligand that is present on all amyloid fibrils. SAP is evolutionarily highly conserved and no polymorphisms or deficiencies have ever been identified. It is expressed constitutively by hepatocytes, has a steady plasma concentration of around 30 mg/l, and a half-life in the circulation of 24 hours. In amyloidosis, circulating SAP exists in a dynamic equilibrium with a much larger extravascular pool of SAP associated with the amyloid deposits. Only SAP molecules in the plasma are subject to catabolism, which occurs in the liver. The universal presence and persistence of SAP in amyloid suggests that it might contribute to the pathogenesis of amyloid, and there are various mechanisms by which this could conceivably occur. On simple thermodynamic grounds alone, pentavalent binding of SAP to amyloid fibrils must have a stabilizing effect. SAP may mask amyloid from recognition and clearance by coating it with a structurally unremarkable autologous protein. In addition, the binding of SAP inhibits digestion of amyloid fibrils by phagocytes and proteinases \textit{in vitro}, presumably reflecting its stabilizing effect and the fact that SAP is itself highly proteinase-resistant. The role of SAP in protecting and promoting amyloid deposition has been confirmed in SAP ‘knock-out’ mice in which experimentally induced AA amyloidosis was substantially reduced.\textsuperscript{8} The physiological roles of SAP appear to include the binding and clearance of DNA and chromatin, which may be released when cells undergo apoptosis.\textsuperscript{9} Some, but not all, amyloid deposits also contain one or more other proteins, including apolipoprotein E, various proteinase inhibitors, complement components and extracellular matrix constituents. The role, if any, of these molecules in pathogenesis and/or effects of amyloid is not known.

There are still many outstanding questions about amyloid deposition. It is not clear why only a relatively small number of unrelated proteins form amyloid \textit{in vivo} when it is becoming increasingly clear that others can be induced to do so \textit{in vitro}. Little is yet known about the genetic or environmental factors that determine individual susceptibility to amyloid, or those that govern its anatomical distribution and clinical effects. There is huge variation not only between the different types of amyloid but also between and even within kindreds with hereditary amyloidosis associated with identical mutations. Only a small fraction of patients with chronic inflammatory disease ever develop AA-amyloidosis, and they can do so at any time from about 12 months to many decades after developing the underlying disorder.\textsuperscript{10} Studies in mice have shown that parenteral injection of a minute extract of amyloidotic material primes them for many months to develop AA-amyloidosis with 1–2 days of receiving a single acute phase stimulus, in contrast to unprimed mice which typically require an inflammatory stimulus for about 6 weeks. The precise component of amyloid that represents this so-called amyloid enhancing factor (AEF)\textsuperscript{11} has not been characterized, but the presence of AEF evidently increases the proportion of precursor proteins that adopt the amyloid conformation, possibly by capturing susceptible transiently unfolded intermediates onto an established ‘amyloid template’. As amyloid itself is extremely rich in AEF, the
conditions necessary for amyloid formation/propagation in vivo appear to be self-perpetuating once an initial nidus of amyloid material has been laid down, thereafter depending only on a continued supply of the respective fibril precursor protein.

**Pathological effects of amyloid**

Amyloid deposits accumulate in the extracellular space, progressively disrupting the normal tissue architecture and impairing organ function. Amyloid deposits can act as both microscopic and macroscopic space-occupying lesions. Although general prognosis and organ dysfunction are inversely related to the amyloid load, there is marked individual variation and for any given quantity of amyloid the resulting degree of organ compromise is unpredictable. Although amyloid may be relatively inert in the sense that it fails to stimulate either a local or systemic host inflammatory response, there is some evidence that the fibrils may exert cytotoxic effects, possibly by promoting local inflammation via RAGE receptors or apoptosis. This is an attractive theory as it could explain how scanty deposits, for example those that occur in the brain in Alzheimer’s disease, cause disease without any histological evidence of inflammation or tissue necrosis. Another strong clinical impression is that active, progressive deposition of new amyloid is associated with accelerated deterioration of organ function compared with relative stability of function in the presence of even large amounts of stable amyloid deposits. This may reflect better adaptation of the host tissues to amyloid that has accumulated very gradually, or relate to particularly toxic properties of transient prefibrillar oligomers.

The natural history of amyloidosis is usually of relentless progression, leading to organ failure and often death. However, the dogma that amyloid deposition is irreversible is incorrect, and clinical progression of the amyloid diseases merely reflects that the deposits are usually being laid down more rapidly than they turning over. Without treatment the conditions that underlie amyloidosis are typically progressive and unremitting, but there are numerous reports describing regression of amyloid when associated inflammatory and other diseases have been controlled. Under favourable circumstances, this is accompanied by stabilization or recovery of organ function, and much improved patient survival.

**Types of amyloid**

**Acquired systemic amyloidosis**

**Reactive systemic, AA-amyloidosis**

This is a complication of chronic inflammation and is the third-most common type of systemic amyloidosis seen in the UK. It is responsible for approximately 10% of the new cases of systemic amyloidosis in the UK each year. The amyloid fibrils are derived from the acute phase reactant, SAA protein. SAA is an apolipoprotein of high-density lipoprotein, which, like CRP is synthesized by hepatocytes under the transcriptional regulation of proinflammatory cytokines, particularly tumour necrosis factor (TNF) α, interleukin-1 (IL-1) and interleukin-6 (IL-6). The median plasma concentration of SAA in health is 3 mg/l, but this can increase to over 2000 mg/l during a brisk acute phase response. The AA protein is derived from circulating SAA by proteolytic cleavage, probably by macrophages. It is not known whether cleavage of SAA occurs before and/or
Amyloidosis can complicate any disorder that stimulates a frequent or prolonged acute phase response. Although sustained overproduction of SAA is a necessary prerequisite for the development of AA-amyloidosis, it is not sufficient as AA-amyloid deposition occurs in a minority of patients with inflammatory diseases. The factors beyond supply of SAA, the amyloid fibril precursor protein, which predispose to development of AA-amyloidosis are largely still unclear but one important contributor appears to be the SAA gene isotype. There are four SAA genes in man, all on chromosome 11. SAA1 and SAA2 are responsible for the acute phase response; SAA4 is expressed constitutively; and SAA3 is a pseudogene. There are a number of isoforms at the SAA1 and SAA2 loci. Susceptibility to AA-amyloidosis is increased among individuals who are homozygous for their SAA1 allele, and studies in Japan suggest that SAA1γ is more inherently amyloidogenic than the α and β isotypes. Similar results have been reported in SAA2 where the allele SAA2α2 is significantly overrepresented in Caucasian patients with AA-amyloidosis complicating juvenile inflammatory arthritis.

Systemic amyloidosis associated with monoclonal immunocyte dyscrasias, AL-amyloidosis

This develops in about 2% of individuals with monoclonal B cell dyscrasias. AL fibrils are derived from the N-terminal region of monoclonal immunoglobulin light chains, which are unique in each patient and which explain the substantial heterogeneity of AL-amyloidosis in terms of organ involvement and overall clinical course. AL proteins are usually derived from all or part of the variable (VL) domain. and their molecular weight varies between about 8000 and 30000 Da. AL is more commonly derived from λ chains than from κ chains, despite the fact that κ chains predominate among both normal immunoglobulins and the paraprotein products of immunocyte dyscrasias. Some amyloidogenic light chains have distinctive amino acid replacements or insertions compared with non-amyloid monoclonal light chains, including replacement of hydrophilic framework residues by hydrophobic ones, changes that can promote aggregation and insolubility. Certain light-chain isotypes, notably VλVI, are especially amyloidogenic, and there is a degree of concordance between some isotypes and their tropism for being deposited as amyloid in particular organ systems. For example, the VλVI isotype often presents with dominant renal involvement, whereas the VλII isotype frequently involves the heart. The inherent ‘amyloidogenicity’ of certain monoclonal light chains has been demonstrated in an in vivo model in which purified Bence Jones proteins were injected into mice. Animals receiving light chains from patients with AL amyloid developed typical amyloid deposits composed of the human protein, whereas animals receiving light chains from myeloma patients without amyloid did not.
AL-amyloidosis may potentially occur in association with any form of monoclonal B cell dyscrasia, including multiple myeloma, Waldenström’s macroglobulinaemia and, occasionally, other malignant lymphomas or leukaemias. However, well over 80% of cases are associated with low-grade and otherwise ‘benign’ monoclonal gammopathies that are often difficult to demonstrate. Histological studies indicate that an element of minor and clinically insignificant amyloid deposition occurs in up to about 10% of patients with myeloma. The cytogenetic abnormalities that commonly occur in multiple myeloma and monoclonal gammopathy of undetermined significance) MGUS, such as 14q translocations and 13q deletion, have also been observed in AL-amyloidosis, but their prognostic significance has not been fully elucidated.29

Dialysis-related amyloidosis (DRA)

β2-microglobulin amyloid deposition was first described in 1980 and occurs in patients with dialysis-dependent chronic renal failure, predominantly in articular and peri-articular structures.30 The amyloid fibril precursor protein is β2-microglobulin, the invariant chain of the MHC class I molecule, which is expressed by all nucleated cells. It is synthesized at an average rate of 2.4 mg/kg/day and is normally filtered freely at the glomerulus and then reabsorbed and catabolized by the proximal tubular cells. Decreasing renal function causes a rise in concentration of approximately 15-fold. DRA has mostly been recognized in the haemodialysis population but it also occurs in patients on peritoneal dialysis (PD). Relatively few patients are maintained on peritoneal dialysis for the 6–10 years required to develop symptomatic β2-microglobulin amyloid, but histological studies of early subclinical deposits suggest that the prevalence of DRA is similar among patients receiving the two modalities of dialysis. Historically, β2-microglobulin amyloid deposits were said to present in 20–30% of patients within 3 years of commencing dialysis for end-stage renal failure, but the incidence seems to have fallen by 80% between the 1980s and 1990s. This may partially reflect better dialysis and use of high flux systems, but it is likely that other factors such as advanced glycation end-products, the proinflammatory effects of bio-incompatible dialysis membranes and endotoxin contamination of the dialysis fluid may all contribute to the formation of clinically overt DRA.31

Senile systemic amyloidosis

This syndrome affects up to 25% of the very elderly, and seemingly never occurs before the age of 60 years. The amyloid fibrils are composed of normal wild-type TTR.32 The deposits are usually sparse and asymptomatic but, occasionally, extensive infiltration of the myocardium causes congestive cardiac failure and may be fatal.

Hereditary systemic amyloidosis

Hereditary systemic amyloidosis caused by deposition of variant proteins as amyloid fibrils has been reported with the following proteins: transthyretin, cystatin C, gelsolin, apolipoprotein AI, apolipoprotein AII, lysozyme and fibrinogen α-chain. These diseases are all inherited in an autosomal dominant pattern with variable penetrance, and may present clinically at any time from the teens to old age, although usually in adult life. By far the most common hereditary amyloidosis is caused by transthyretin variants and
usually presents as familial amyloid polyneuropathy with peripheral and autonomic
neuropathy. Thus, far more than 100 amyloidogenic TTR mutations have been
described and there are almost certainly many more.³³ Cystatin C amyloidosis presents
as cerebral amyloid angiopathy with recurrent cerebral haemorrhage and clinically
silent systemic deposits, and has been reported only in Icelandic families. Gelsolin
amyloidosis presents with cranial neuropathy but there are also systemic deposits; it is
also extremely rare.³⁴ Hereditary non-neuropathic systemic amyloidosis was first
described by Ostertag in 1932. It is now recognized to be caused by mutations in the
apolipoprotein AI and AII, lysozyme or α-fibrinogen genes.³⁵ The amyloid deposits in
these syndromes can affect any or all of the major viscera, with renal involvement usually
being prominent, although apolipoprotein AI and fibrinogen amyloid occasionally
also manifest with neuropathy. Increasing numbers of patients with hereditary amyloid
have been identified and the disease can easily be misdiagnosed as AL amyloidosis.³⁶

Localized amyloidosis

Localized amyloid deposition is not uncommon, although often undiagnosed, and
reportedly accounts for 9.3% of all amyloidosis.³⁷ It results either from local produc-
tion of fibril precursors, or from properties inherent to the particular microenviron-
ment, which favour fibril formation of a widely distributed precursor protein. The vast
majority of deposits are AL in type, and symptomatic deposits occur most frequently
in the eye, skin, gastrointestinal, respiratory or urogenital tracts.³⁸ They are often asso-
ciated with extremely subtle focal monoclonal B cell proliferation confined to the
affected site and surgical resection of these localized ‘amyloidomas’ can sometimes be
curative. Symptomatic apparently localized amyloid deposits can rarely be manifesta-
tions of systemic disease and patients should always be fully investigated to exclude
more generalized amyloid deposition.³⁹ Progression from localized to systemic amy-
loidosis is very rare.

Cerebral amyloidosis

The brain and intracerebral blood vessels are usually spared in systemic amyloidosis
but are important sites for local deposition of amyloid. The best characterized form of
cerebral amyloid is that related to Alzheimer’s disease, the most common form of
dementia worldwide. The fibril protein in the intracerebral and cerebrovascular amyloid
of Alzheimer’s disease, Down’s syndrome and hereditary amyloid angiopathy of Dutch
type is known as β-protein. This 39–43 residue sequence is cleaved from β-amyloid
precursor protein (APP). There is now mounting evidence that cerebral amyloid
deposition is directly neurotoxic but the exact mechanisms leading to neuronal degen-
eration have yet to be elucidated. There is mounting evidence that relatively low
molecular amyloid aggregates, as opposed to mature fibrils, may have a major part in
the pathogenesis of this disorder.

Diagnosis

Diagnosis of amyloid relies on a high index of clinical suspicion. Unfortunately, amyloid
is frequently asymptomatic until a relatively late stage and can then present with highly
variable or non-specific symptoms. The protean manifestations of systemic amyloid depend on the predominant organs affected and can include symptoms and signs referable to any system except the central nervous system.

**Histology**

The diagnosis of amyloidosis generally requires histological confirmation.\(^4^0\) Biopsy of a clinically affected visceral organ, for example the kidney, liver or heart, is usually diagnostic but gives no information about the total body amyloid load or the distribution of deposits in other organs. Biopsy can be hazardous as there is an increased risk of haemorrhage and significant bleeds have been reported in 5% of liver biopsies. This is attributable to the increased fragility of affected blood vessels, reduced elasticity of severely amyloidotic organs and, very occasionally in AL-type, to an acquired deficiency of clotting factors IX and X. A less invasive alternative in suspected systemic disease is fine-needle aspiration of subcutaneous fat, or rectal or labial salivary gland biopsy. In skilled hands these ‘screening’ biopsies can produce positive results in up to 80% of cases, but in routine practice sensitivity is only about 50%.

The identification of amyloid depends on the pathognomonic red-green dichroism observed when tissue stained with the aniline dye Congo red is viewed under cross-polarized light\(^4^1\) (Fig. 18.1a and 18.1b). This optical effect is produced by alignment of the dye molecules along the fibrils. Binding of thioflavin T usually corresponds with Congo red birefringence but is less specific. Congo red staining for amyloid is not a very sensitive test and requires the presence of an adequate amount of amyloid, use of sufficiently thick tissue sections, technically correct staining and visualization procedures, and adequate observer experience. In negatively stained electron microscopy amyloid fibrils are usually about 10–15 nm in diameter, straight, rigid, non-branching, of indeterminate length and composed of twisted protofibrils.

Positive histology for amyloid must be followed-up by immunohistochemistry to determine the fibril protein type.\(^3^9\) Suitable antibodies are widely available but, although immunohistochemistry usually yields definitive results in AA-amyloidosis, it is frequently not diagnostic with AL deposits. Expertise in the immunohistochemical typing of hereditary amyloid is restricted, and definitive immunohistochemical typing of amyloid deposits cannot always be achieved.\(^4^2\) Direct sequencing of extracted isolated fibrils permits identification of the amyloid type, as does laser microdissection and mass spectrometry,\(^4^3\) but these techniques are not yet widely available.

There are a number of problems inherent in histological-based diagnoses; tissue samples must be adequate and there is an unavoidable element of sampling error. This means that biopsies cannot satisfactorily reveal the extent or distribution of amyloid and failure to demonstrate amyloid cannot exclude the diagnosis. Many of these problems can be overcome by combining histological examination of biopsy material with whole-body SAP scintigraphy.

**SAP scintigraphy**

SAP is a highly conserved, invariant plasma glycoprotein of the pentraxin family that becomes specifically and highly concentrated in amyloid deposits of all types as a result
of its calcium-dependent binding to amyloid fibrils. Radiolabelled SAP scintigraphy has been used since 1988 at the UL National Amyloidosis Centre for diagnosis and quantitative monitoring of amyloid deposits. This safe non-invasive method provides information on the presence, distribution and extent of visceral amyloid deposits, and serial scans monitor progress and response to therapy (Fig. 18.2a and 18.2b). Unfortunately, the method is not informative about amyloid deposition in the moving heart and is not commercially available.

Fig. 18.1 Typical Congo Red histology. The same tissue section viewed under conventional microscopy demonstrating congophilic amyloid deposits (a) and under bipolarized light demonstrating the pathognomonic apple green birefringence (b).
**Cardiac imaging**

Cardiac amyloidosis is best evaluated by a combination of echocardiography and electrocardiography (ECG). Two-dimensional Doppler echocardiography classically reveals concentric biventricular wall thickening with a restrictive filling pattern. Amyloid causes diastolic dysfunction with well-preserved contractility until a very late stage. The ECG may be normal in patients with substantial cardiac amyloidosis, but in advanced disease commonly shows small voltage, pathological ‘Q’ waves (pseudo-infarct pattern). Recent developments in magnetic resonance imaging can also contribute to assessment of the severity of cardiac amyloidosis, as can serum assays of the cardiac bio-markers, N-terminal-pro BNP and troponin T.

**DNA analysis**

Hereditary amyloidoses are rare, and the diagnosis can all too easily be overlooked. Although all types are dominantly inherited, penetrance is highly variable, and successful immunohistochemical typing depends heavily on tissue fixation, antibody preparations,

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**Fig. 18.2** Posterior whole-body scintigraphic images following intravenous injection of I-123-labelled human serum amyloid P component (SAP) showing the typical appearances of AL-amyloidosis with abnormal tracer uptake into amyloid deposits in the liver, spleen and bone marrow (a) and AA-amyloid with deposits in the spleen, kidneys and adrenal glands (b).
inclusion of comprehensive absorption and tissue controls and technical experience. In practice, definitive immunohistochemical typing of hereditary amyloidosis quite frequently cannot be obtained. Patient prognosis and treatment are entirely dependent on the nature of the precursor protein, and DNA analysis is now mandatory in all patients with non-AA-systemic amyloidosis that cannot be confirmed absolutely to be AL-type. Several, or indeed many, amyloidogenic mutations have been identified in most of the genes associated with hereditary amyloidosis and new variants are regularly identified. It is therefore best to carry gene sequencing rather than to use methods such as restriction fragment length polymorphism (RFLP), which are directed at individual known mutations.

Investigation of the underlying disease

The process underlying amyloid deposition needs to be sought and characterized in each case (see Chapter 19).

References

Chapter 19

Amyloidosis: Rheumatic disease and amyloid; clinical features and treatment

H.J. Lachmann and P.N. Hawkins

Introduction
Most of the clinical features of amyloid are non-specific, malaise and weight loss are frequent early symptoms and, although a high index of suspicion may prompt investigation, the diagnosis of systemic amyloidosis often remains an unexpected biopsy finding. Even after a diagnosis of amyloidosis has been confirmed, subsequent identification of amyloid type may not be straightforward. Definitive diagnosis relies on a combination of clinical features, underlying conditions, histology, immunohistochemistry and, where available, more specialized but highly informative investigations such as SAP scintigraphy, DNA analysis and proteomics. It is unwise to rely on any of these in isolation given the limitations in their sensitivity and specificity, and the possibility that a condition that may be associated with amyloidosis, such as a inflammatory arthritis, monoclonal gammopathy or an amyloidogenic mutation, might be an entirely incidental finding. Clinical evaluation of a patient with amyloidosis must always extend to a thorough characterization of the underlying disorder as treatment of the latter remains the prime objective of management.

General treatment principles
Although amyloid deposits are not irreversible, they do turn over relatively slowly and the natural history of amyloidosis is that the rate of fibril deposition usually exceeds that of mobilization. As a result, the amyloid diseases tend to be progressive. Amyloid will regress if either its rate of deposition is slowed or its clearance is enhanced. Although novel therapies with the latter aim are under development, at present the treatment of all types of amyloid centres on reducing the supply of the amyloid precursor protein and supporting or replacing compromised organ function. Self evidently, treatment depends completely on precise identification of the amyloid fibril type.

Preservation and replacement of organ function
Organs that are extensively infiltrated by amyloid may fail precipitously with little or no warning, and seemingly without provocation, even when organ function has previously been entirely normal. Scrupulous attention needs to be paid to salt and water balance,
maintenance of the circulating volume and prompt treatment of sepsis to reduce the risk of acute organ failure at all times, and even more so during immunosuppressive treatment. For these reasons potentially nephrotoxic drugs, elective surgery and general anaesthesia are best avoided in patients with systemic amyloidosis unless there are compelling indications.

Significant renal impairment and/or nephrotic syndrome are present at diagnosis in approximately 75% of patients with systemic amyloidosis. The oedema of nephrotic syndrome generally requires treatment with loop diuretics. These may need to be in high doses and resistant cases may require addition of thiazide and/or potassium-sparing diuretics. Salt and, in many cases, fluid restriction may be advisable. In patients who have difficulty maintaining their intravascular volume infusions of salt, poor human albumin can be very helpful.

Hypertension is relatively unusual but should be treated aggressively and treatment of hypercholesterolaemia should also be considered. There is a theoretical risk of thrombosis in patients with amyloidosis and nephrotic syndrome but in practice this is not frequent.

In some cases the kidneys are so badly compromised that, without replacement of their function, patients will not survive treatment, or live long enough to derive benefit from it. It is usually feasible to manage this with renal replacement therapy in the form of haemodialysis or peritoneal dialysis. The outcome of AL-amyloidosis patients on long-term dialysis is improving but remains about 70% of that in other age-matched non-diabetic patients. The outcome of patients with other types of amyloid is often more favourable. Transplantation has been performed in a number of patients and although early post-transplant mortality is increased, due to sepsis and cardiac failure, long-term graft survival and rejection rates compare very well with patients with other systemic diseases. Most amyloid patients have a functioning graft until death, even though amyloid deposition in the transplanted organ is well recognized.

Cardiac involvement occurs in 30–50% of patients with AL-amyloidosis; it is a major cause of morbidity and is associated with very poor prognosis. Significant cardiac amyloid infiltration on imaging and poor performance status are especially poor prognostic factors and, regrettably, afflicted patients rarely survive long enough to benefit from chemotherapy. The mainstay of treatment for congestive heart failure are loop diuretics often with the addition of spironolactone. As amyloid infiltration causes a restrictive cardiomyopathy, cardiac output depends on relatively high filling pressures. It has not been established whether angiotensin-converting enzyme inhibitors are beneficial, but low cardiac output or orthostatic hypotension frequently limit their use. Calcium-channel blockers and β-blockers are contraindicated in cardiac amyloidosis. Digoxin may cause toxicity at therapeutic levels but is not necessarily contraindicated in the management of patients with atrial fibrillation. Amiodarone is also widely used as an anti-arrhythmic. Prevention of sudden death is difficult and a recent study suggests that the majority of patients with severe cardiac amyloidosis will not benefit from implantable cardioverter-defibrillators as electromechanical dissociation rather than arrhythmia appears to be the cause of death.

In younger patients with advanced irreversible cardiac failure without significant other organ involvement, heart transplantation offers a possibility of long-term survival.
Cardiac transplantation has been performed in a small number of patients, although the procedure remains controversial because of the scarcity of donor hearts, the high transplant-related mortality (due to subclinical extracardiac amyloid) and the likelihood of subsequent amyloid deposition in the graft. Subsequent chemotherapy, usually high-dose melphalan and autologous stem cell transplantation, is required to prevent recurrence of cardiac AL-amyloid or its progression in other organ systems. In some types of hereditary amyloidosis a liver transplant may be required as ‘surgical gene therapy’ to prevent further synthesis of the amyloidogenic variant protein.

**Reactive systemic, AA, amyloidosis**

**Associated conditions**

The list of chronic inflammatory, infective and neoplastic disorders that can be complicated by AA-amyloidosis is extensive (Table 19.1), and the predominant aetiology varies among different countries. In the Western world the most common predisposing conditions are the chronic inflammatory arthritides, which account for 60% of cases. Chronic infections are the major underlying cause in the developing world but account for only 15% of cases in the UK. Amyloidosis occurs exceptionally rarely in systemic lupus erythematosus and ulcerative colitis, reflecting the unusually modest acute phase response evoked by these particular conditions. AA-amyloidosis can complicate Castleman’s disease, a cytokine-producing tumour that secretes interleukin (IL)-6.

The inherited fever syndromes, which are rare autoinflammatory syndromes, carry an exceptionally high risk of complication by AA-amyloid deposition. These diseases include familial Mediterranean fever (FMF), TNF receptor associated periodic syndrome (TRAPS), cytopyrin associated periodic syndrome (CAPS) and mevalonate kinase deficiency (MKD). All present early in life and clinical attacks are accompanied by a very striking acute phase response in which the peak SAA level may exceed 2000 mg/l. The pattern of lifelong recurrent attacks accompanied by a massive increase in the supply of a potential amyloid precursor protein probably provides the explanation for the striking relative risk of AA amyloidosis in these diseases, and there are data to suggest that the availability of effective disease control in the form of colchicine in FMF has reduced the risk of developing amyloidosis from 75% to 13%. The availability of highly specific cytokine-blocking agents has produced dramatic responses in CAPS, and to a lesser extent in TRAPS and MKD. The median latency between onset of inflammation and diagnosis of amyloid is approximately 17 years for all of the major underlying disease groups, although some individuals develop clinically significant amyloid in less than 12 months and others only after many decades. The median age at diagnosis is 50 years. Presentation in childhood, although becoming less common, is still recognized and at the other extreme patients may not develop clinical amyloidosis until their ninth decade.

As with all types of amyloidosis, AA appears slightly more common in men who account for 56% of the largest characterized series. This is particularly striking given that rheumatoid arthritis is a disease with a marked female predominance. In the large series from the UK there was significant overrepresentation of ethnic groups originating from the eastern Mediterranean and an underrepresentation of people of African origin.
### Table 19.1 Conditions associated with AA-type amyloidosis

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<th>Chronic inflammatory arthritides</th>
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<tr>
<td>Rheumatoid arthritis</td>
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<td>Juvenile inflammatory arthritis</td>
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<td>Ankylosing spondilitis</td>
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<td>Psoriatic arthropathy</td>
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<td>Reiter’s syndrome</td>
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<td>Adult Still’s disease</td>
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<td>Polyarteritis nodosa</td>
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<td>Behcet’s disease</td>
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<td>Systemic lupus erythematosus</td>
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<td>Polymyalgia rheumaticana</td>
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<td>Crohn’s disease</td>
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<td>Ulcerative colitis</td>
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<th>Periodic fevers</th>
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<td>Familial Mediterranean fever</td>
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<td>Muckle-Well’s syndrome</td>
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<td>Familial cold urticaria</td>
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<td>TNF receptor-associated periodic syndrome</td>
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<td>Hyperimmunoglobulin D syndrome</td>
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<th>Chronic microbial infections</th>
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<td>Leprosy</td>
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<td>Tuberculosis</td>
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<td>Bronchiectasis</td>
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<th>Chronic cutaneous ulcers</th>
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<td>Chronic pyelonephritis</td>
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<td>Osteomyelitis</td>
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<td>Subacute bacterial endocarditis</td>
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<td>Whipples disease</td>
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<th>Neoplasia</th>
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<td>Hodgkin disease</td>
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<td>Renal cell carcinoma</td>
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<td>Adenocarcinoma of the lung, gut, urogenital tract</td>
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<td>Basal cell carcinoma</td>
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<td>Hairy cell leukaemia</td>
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<td>Castleman’s disease</td>
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<td>Hepatic adenoma</td>
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The relative paucity of AA amyloidosis in Americans of African origin has previously been noted. This does not appear to be due to protection from amyloidosis in general, and may be due to the relatively low number of patients of African ancestry who suffer from rheumatoid arthritis or to the lack of other factors predisposing to AA-amyloidosis in general, such as SAA type. The exact prevalence of AA-amyloidosis is unclear. Biopsy and post-mortem series suggest that the prevalence of AA-amyloidosis in patients with chronic arthritides is between 3.6% and 5.8%. An observation that remains unexplained is that the incidence of AA-amyloid is much lower in the USA than in Europe and Scandinavia, and, perhaps by the same, as yet unknown, mechanisms, its prevalence in Europe is believed to have decreased substantially over the past 40 years.

Clinical features

AA-amyloid deposition can be extensive without causing symptoms. The predominant clinical manifestations of AA amyloidosis are renal and more than 97% of patients present with proteinuric kidney dysfunction. Haematuria, tubular defects and diffuse renal calcification occur rarely. Just over 50% of patients have nephrotic syndrome at presentation. Approximately 10% of patients are at end-stage renal failure when the diagnosis is made but, although 75% of patients present with an eGFR of greater than 30 ml/min, over 40% eventually progress to end-stage kidney failure.

SAP scintigraphy has shown that the spleen is infiltrated in almost all cases and the adrenal glands in at least a third, although clinical hypoadrenalism is not common. The liver and gut are also frequent sites of AA-amyloid deposition and hepatosplenomegaly is present in 9% of cases at presentation. Hepatic failure due to AA-amyloidosis is exceptionally rare and gut motility disorders and malabsorption do occur but only in advanced disease. Cardiac amyloidosis is usually only clinically overt in patients with advanced disease and established renal failure. Neurological involvement is also atypical and autonomic neuropathy does not appear to be a common feature.

Table 19.1 (continued) Conditions associated with AA-type amyloidosis

<table>
<thead>
<tr>
<th>Other</th>
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<td>Intravenous and subcutaneous drug abuse</td>
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<td>Hypogammaglobulinaemia</td>
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<td>Cyclic neutropaenia</td>
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<td>Common variable immunodeficiency</td>
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<td>Hyperimmunoglobulin M syndrome</td>
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<td>Cystic fibrosis</td>
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<td>Kartagener’s syndrome</td>
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<tr>
<td>Epidermolysis Bullosa</td>
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<tr>
<td>Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome</td>
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Treatment

As the fibril precursor protein in AA-amyloidosis is the acute phase reactant SAA, the aim of treatment is sustained and complete control of the underlying inflammatory disease process. The choice of therapy depends on the nature of the underlying disease process but therapeutic success must always be assessed by the long-term control of the hepatic acute phase response proteins, ideally SAA and otherwise CRP. Median SAA levels have been shown to be strongly associated with outcome, but SAA measurement is available only in a relatively limited number of research laboratories. Median CRP also predicts clinical outcome and can be used as a surrogate marker of SAA provided its values are interpreted with some caution. CRP and SAA rise and fall in parallel but some patients may have five or even tenfold SAA bias, and as a result, although elevated levels of median CRP are strongly associated with a poor outcome, apparently normal levels may be falsely reassuring in a minority of patients whose SAA concentrations are significantly higher.

Most patients with inflammatory arthritis have previously failed to respond to conventional disease-modifying anti-rheumatoid drugs, such as methotrexate, and many do well with anti-TNF therapies or other biologicals such as anti-CD20 antibodies or anti-IL-1 or IL-6 therapies. In patients who fail to respond to these agents there may still be a role for therapy with alkylating agents such as chlorambucil or cyclophosphamide. Treatment of chronic sepsis is based on long-term appropriate anti-microbials and sometimes combined with surgical debridement or excision of infected tissue. In patients with long-term drug addiction, eradication of skin sepsis needs to be combined with support to enable them to stop self-injecting with contaminated apparatus or drugs. Crohn’s disease often responds to conventional immunosuppression or infliximab. Castleman’s disease, a rare IL-6-secreting tumour, can sometimes be completely excised, and in those cases where surgery is not feasible or curative there is evidence of benefit for anti-IL-6 therapies. The 6% of patients in whom the underlying inflammatory disease cannot be identified are a serious management challenge and therapy in these cases has to be empirical and guided by frequent assays of SAA.

More than 40% of patients will eventually require renal replacement therapy and survival on dialysis is now comparable with that of non-diabetic associated end-stage renal failure, although earlier series reported less good outcomes. Recent experience of renal transplantation in selected patients has been encouraging with long-term graft and patient survival exceeding that set by British and American standards. The encouraging outcomes in patients whose underlying disease can be controlled has resulted in some cases receiving living donor renal transplants.

Systemic amyloidosis associated with immunocyte dyscrasia, AL-amyloidosis

Associated conditions

Systemic AL, formerly known as ‘primary’, amyloidosis occurs in about 2% of individuals with monoclonal B cell dyscrasias. The B cell dyscrasias underlying systemic AL-amyloidosis can include almost any clonal proliferation of differentiated B lymphocytes, including
multiple myeloma, Waldenström’s macroglobulinaemia and occasionally other malignant lymphomas or chronic leukaemias but the vast majority, over 80%, of cases are associated with low-grade and otherwise ‘benign’ monoclonal gammopathies. Indeed, in some cases deposition of AL-amyloid may be the only evidence of the dyscrasia. On the other hand, low-grade monoclonal gammopathies occur in up to 8% of the older population,\textsuperscript{42} and their presence in a patient with amyloidosis may be completely incidental.

**Clinical features**

Systemic AL-amyloidosis accounts for about one in 1500 deaths in Britain and occurs equally in men and women. The age-adjusted incidence of AL-amyloidosis in the USA has been estimated to be between 5.1 and 12.8 per million persons per year, which is equivalent to approximately 3000 new cases per year. The median age at presentation is 65 years, but it can occur in young adults and is probably underdiagnosed in the elderly, in whom monoclonal gammopathies are most prevalent.

The clinical features of AL amyloidosis are protean,\textsuperscript{43} as almost any organ other than the brain parenchyma can be directly involved. Although certain clinical features are very strongly suggestive of AL-amyloidosis, and multiple vital organ dysfunction is common, many patients present with non-specific symptoms such as fatigue and weight loss. Cardiac involvement is overt in 30% of patients at presentation and is the ultimate cause of death in more than 50%. It usually presents as congestive cardiac failure due to a restrictive cardiomyopathy but may also cause arrhythmias and angina. Renal AL-amyloidosis has the same manifestations as renal AA-amyloidosis, but the prognosis is worse. Gut involvement may cause motility disturbances (often secondary to autonomic neuropathy), malabsorption, perforation, haemorrhage or obstruction. Macroglossia occurs in only about 10% but is almost pathognomonic of AL type (Fig. 19.1). Hyposplenism sometimes occurs in both AA- and AL-amyloidosis. Painful sensory polyneuropathy with early loss of pain and temperature sensation followed later by motor deficits is seen in 10–20% of cases and carpal tunnel syndrome in 20%.

![Fig. 19.1 Infiltration of soft tissues by AL-amyloid producing macroglossia.](image)
Autonomic neuropathy leading to orthostatic hypotension, impotence and gastrointestinal disturbances may occur alone or with peripheral neuropathy, and carries a very poor prognosis. Skin involvement is common and usually takes the form of bruising either spontaneously or after minimal trauma. Periorbital ecchymosis is a feature of AL-amyloidosis (Fig. 19.2). A rare but serious manifestation of AL-amyloid is an acquired bleeding diathesis that may be associated with deficiency of factor X and sometimes also factor IX, or with increased fibrinolysis. Articular amyloid is rare but may superficially mimic acute polyarticular rheumatoid arthritis, or may present as asymmetrical arthritis affecting the hip or shoulder. Infiltration of the glenohumeral joint and surrounding soft tissues occasionally produces the characteristic ‘shoulder pad’ sign. Nail dystrophy is a rare but recognised feature of amyloidosis (Fig. 19.3).
SAP scan appearances are much more heterogeneous than those seen in AA type and any pattern of organ distribution may be seen. The only distinctive feature is bone marrow involvement, which occurs in approximately 30% of cases and is pathognomonic of AL type.

Although AL amyloid is a progressive systemic disease, its clinical course is often punctuated by step-wise deteriorations, often terminating in multi-system failure. The lack of obvious disease progression from one clinic visit to the next may be falsely reassuring, and in the very extensive Mayo Clinic experience, comprising over 400 cases of AL-amyloidosis, median survival was only 12–15 months and was even less when associated with multiple myeloma. Although survival has improved with better chemotherapy, median survival remains about 6 months in cases where frank heart failure is evident at presentation. Other very poor prognostic factors include hyperbilirubinaemia, autonomic neuropathy and a large whole body amyloid load on SAP scintigraphy.

**Treatment**

The aim of treatment in AL-amyloidosis is to suppress proliferation of the underlying B cell clone and, therefore, production of the amyloid fibril precursor protein, monoclonal immunoglobulin light chains. There are, however, many difficulties: chemotherapy regimes are based on those used in multiple myeloma, but the plasma cell dyscrasias in most AL patients are relatively low grade and may be less chemosensitive; diagnosis is difficult and can be delayed and many patients have advanced multi-system disease, which limits their treatment options. Regression of amyloid is a gradual process, which may not lead to measurable clinical improvement or recovery of organ function for many months, or even years, after successful suppression of the causative plasma cell dyscrasia. Mobilization of amyloid from the heart is much slower than from the liver or kidneys, and patients with cardiac dysfunction may not live long enough to benefit from chemotherapy, even when it has suppressed their clonal disease. Nonetheless, many patients with AL amyloidosis do benefit substantially from chemotherapy.

The ability to monitor the underlying clone using sensitive assays that detect free immunoglobulin light chains has been a major advance, which permits early identification of a clonal response and potentially individually tailored treatment. Prolonged low-intensity cytotoxic regimes such as oral melphalan and prednisolone are beneficial in about 20% of patients and have now been superseded by combination chemotherapy regimes such as cyclophosphamide, thalidomide and dexamethasone or melphalan and dexamethasone as these have much higher clonal response rates. These can be further improved with newer agents such as bortezomib or lenalidomide, which show promising early results. Autologous stem cell transplantation has been the treatment of choice, particularly in the USA and is associated with high complete response rates. However, very rigorous patient selection for high-dose chemotherapy is essential because the procedure mortality is high in individuals with multiple amyloidotic organ involvement, especially patients with autonomic neuropathy, severe cardiac amyloidosis or a history of gastrointestinal bleeding, and in those aged over 55 years. Indeed, the only randomized controlled study comparing autologous transplantation with lower dose treatment was terminated early as patient mortality
was higher in the transplanted group, although both the study design and findings were somewhat contentious.60

**Dialysis-related amyloidosis (DRA), β2-microglobulin amyloidosis**

**Associated conditions**
The amyloid fibril precursor protein β2-microglobulin is the invariant chain of the MHC class 1 molecule, which is expressed by all nucleated cells. It is synthesized at an average rate of 150–200 mg/day and in normal circumstances is freely filtered at the glomerulus and then reabsorbed and catabolized by the proximal tubular cells.61 Decreasing renal function is accompanied by a rise in levels. β2-microglobulin amyloidosis was first described in 198062 and occurs in patients who have been on dialysis for several years, or very occasionally in individuals with longstanding severe chronic renal impairment. Relatively few patients have been maintained on peritoneal dialysis for the 5–10 years required to develop symptomatic β2-microglobulin amyloid, but histological studies of early subclinical deposits suggest that the incidence of DRA is similar among patients receiving the two dialysis modalities. Indeed, β2-microglobulin amyloid deposits have been reported in 20–30% of patients within 3 years of commencing dialysis for end-stage renal failure.63

**Clinical features**
β2-microglobulin amyloidosis is preferentially deposited in articular and peri-articular structures, and its manifestations are largely confined to the locomotor system.64 Carpal tunnel syndrome is usually the first clinical manifestation. Some individuals develop symptoms within 3–5 years and by 20 years the prevalence is almost 100%.65 Older patients appear to be more susceptible to the disease, and tend to exhibit symptoms more rapidly.65 Amyloid arthropathy tends to occur a little later but eventually affects the most patients on dialysis. The arthralgia of β2-microglobulin amyloidosis affects the shoulders, knees, wrists and small joints of the hand and is associated with joint swelling, chronic tenosynovitis and, occasionally, haemarthroses. Spondylarthropathies are also well recognized, as is cervical cord compression. β2-microglobulin amyloid deposition within the peri-articular bone produces typical appearances of subchondral erosions and cysts, which can contribute to pathological fractures particularly of the femoral neck, cervical vertebrae and scaphoid. Although β2-microglobulin amyloidosis is a systemic form of amyloid, manifestations outside the musculoskeletal systemic are rare, but there have been reports of β2-microglobulin amyloidosis causing congestive cardiac failure, gastrointestinal bleeding, perforation or pseudo-obstruction and macroglossia.66,67

**Treatment**
The only really effective treatment for DRA is successful renal transplantation. Serum levels of β2-microglobulin fall rapidly following transplantation and this is usually accompanied by a very rapid and substantial improvement in symptoms. Although prospective...
SAP scintigraphy has shown that $\beta_2$-microglobulin amyloid deposits can gradually regress, the resolution of DRA symptoms within days or weeks of renal transplantation implicates other factors. This probably include the anti-inflammatory properties of immunosuppression after transplantation, and some effect of discontinuation of the dialysis procedure itself, perhaps through a decrease in advanced glycosylation end products and RAGE-mediated inflammation.\textsuperscript{68} In contrast to the symptoms, radiological bone cysts heal very slowly indeed,\textsuperscript{69} and unsurprisingly amyloid can be demonstrated histologically many years after renal transplantation. Within a few years of renal transplantation, symptoms of DRA may reappear very rapidly if the graft is lost, providing further evidence that dialysis is required for the clinical expression of disease associated with $\beta_2$-microglobulin amyloid deposits.

Attempts have been made to reduce $\beta_2$-microglobulin levels and DRA by altering the dialysis prescription. There is some evidence that the risks of DRA are increased in patients dialysed using less ‘biocompatible’ cuprophane membranes, and that use of the more permeable membrane systems is relatively protective.\textsuperscript{70} Greater removal of $\beta_2$-microglobulin is attained in patients undergoing high-flux haemodiafiltration and in the long term these patients may be less prone to DRA.\textsuperscript{71} In addition, the incidence of DRA seems to be falling, perhaps linked to fewer contaminants in the dialysate.\textsuperscript{72}

Drug treatment of established DRA includes non-steroidal anti-inflammatory analgesics, systemic and intra-articular corticosteroid therapy, but none of these is especially effective. Surgery may be required to relieve carpal tunnel compression, stabilize the cervical spine or treat bone fractures.

### Hereditary amyloidosis

**Familial amyloidotic polyneuropathy (FAP)**

This is caused by point mutations in the gene for the plasma protein transthyretin (TTR)\textsuperscript{73} and is an autosomal dominant syndrome with peak onset between the third and sixth decades. The disease is characterized by progressive and disabling peripheral and autonomic neuropathy and varying degrees of visceral amyloid involvement. Severe cardiac amyloidosis is common and when this predominates the disease is known as familial amyloid cardiomyopathy (FAC). Deposits within the vitreous of the eye are recognized and renal, thyroid, spleen and adrenal deposits are usually subclinical. There are well-recognized disease foci in Portugal, Japan and Sweden, and FAP has been reported in most ethnic groups throughout the world. There is considerable phenotypic variation in the age of onset, rate of progression, involvement of different organ systems and disease penetrance generally, although within families the pattern is often quite consistent. More than 100 variant forms of TTR are associated with FAP, the most frequent of which is the substitution of methionine for valine at residue 30.

**Treatment.** Until the 1990s, the treatment of FAP was limited to supportive measures to help with malnutrition, bladder and bowel dysfunction, hypotension and renal and cardiac complications. Most patients died within 5–15 years of diagnosis. Orthotopic liver transplantation was introduced in 1991.\textsuperscript{74} The procedure results in a rapid and near total replacement of the variant protein by donor wild-type TTR, as almost all circulating TTR is produced by the liver. Most FAP patients who have liver
transplants experience a symptomatic improvement within 6–12 months, and successful liver transplantation has now been reported in hundreds of patients with the common V30M mutation. Although the peripheral neuropathy usually only stabilizes, autonomic function can improve substantially and the associated visceral amyloid deposits have been shown by serial SAP scintigraphy to regress in most cases. Important questions remain about the timing of the procedure but, so far, early intervention seems advisable.

Disappointingly in a few cases, there is evidence that wild-type TTR may continue to be deposited after liver transplantation, on the existing ‘template’ of amyloid. This may occur to a clinically important extent in the heart and the vitreous, but seems to be mutation-specific and fortunately seems not to happen in the bulk of FAP patients who have the TTR Met30 variant. More recent work has focused on pharmacological strategies to stabilize the TTR tetramer and prevent its dissociation, a necessary preliminary to amyloid formation. Clinical trials are under way with the non-steroidal anti-inflammatory drug, diflunisal; a novel agent tafamidis has been reported in clinical studies to stabilize TTR and slow progression of neuropathy in FAP due to TTR Met 30 (unpublished data) and there are other novel small molecule pharmaceuticals, which stabilize TTR under development. In addition, there has been interest in the role of inhibitory RNA in preventing expression of the variant TTR.

FAP with predominant cranial neuropathy

Originally described in Finland but also reported in other ethnic groups, this is a very rare autosomal dominant form of hereditary amyloidosis that presents in adult life with cranial neuropathy, lattice corneal dystrophy and a mild distal peripheral neuropathy. There may be skin, renal and cardiac manifestations but these are usually covert, and life expectancy approaches normal. The mutant gene responsible encodes a variant form of gelsolin, which is an actin-modulating protein. The functional role of circulating gelsolin is unknown but may be related to clearance of actin filaments released by apoptotic cells. There is no specific treatment for this disorder, which is progressively disfiguring and very distressing in its late stages.

Hereditary non-neuropathic systemic amyloidosis

Ostertag first described hereditary renal amyloidosis [HRA] in 1932. This syndrome is now known to be associated with mutations in the genes for lysozyme, apolipoprotein A1, apolipoprotein A2 and fibrinogen A α chain. Lysozyme. Hereditary non-neuropathic systemic amyloidosis has been described in association with two lysozyme variants, the substitution of histidine for aspartic acid at position 67, and threonine for isoleucine at position 56. Most patients present in middle age with proteinuria, slowly progressive renal impairment and sometimes hepatosplenomegaly with or without purpuric rashes. Virtually all patients have substantial gastrointestinal amyloid deposits, and, although these are often asymptomatic, they are important as gastrointestinal haemorrhage or perforation is a frequent cause of death in these patients.

Lysozyme is a ubiquitous protein that is produced diffusely within the body and this type of amyloidosis is not therefore ameliorated by liver transplantation. However, the
disease usually runs an extremely slow course, and patients with renal failure merit strong consideration for renal transplantation.

**Apolipoprotein A1.** Apolipoprotein A1 is a major constituent of high-density lipoprotein (HDL). Depending on the mutation, patients can present with massive abdominal visceral amyloid involvement, predominant cardiomyopathy or an FAP-like syndrome. The majority of patients eventually develop renal failure but, despite extensive hepatic amyloid deposition, liver function usually remains well preserved. Renal transplantation offers most patients with this disease an excellent quality of life and prolonged survival, and some patients have had renal grafts for over 20 years without evidence of recurrent amyloidosis or any reduction in graft function.

Approximately half of the apolipoprotein A1 in the circulation is synthesized in the liver, and only one patient with hereditary apolipoprotein A1 amyloidosis has undergone liver transplantation. The reduction by 50% in the plasma concentration of variant apolipoprotein A1 appeared to be sufficient to facilitate regression of his amyloid deposits generally, and supports the use of liver transplantation in patients with this type of amyloidosis who develop hepatic dysfunction.  

**Fibrinogen A α-chain.** This was first isolated from amyloid fibrils in 1993. A total of six amyloidogenic mutations have been described. These include two frame shift mutations, one a single nucleotide deletion in the third base of codon 524, and the other a deletion at codon 522, both of which result in premature termination of the protein at codon 548, and a leucine for arginine substitution at codon 554. However, much the most common mutation results in the substitution of valine for glutamic acid at position 526. We have shown that this mutation is unexpectedly frequent in the northern European population, and that it has variable penetrance. Patients with this form of hereditary amyloidosis frequently do not give a family history of similar disease and are readily misdiagnosed as having acquired AL-amyloid. Most patients present in middle age with proteinuria or hypertension and over the following 4–10 years progress to end-stage renal failure. Amyloid deposition is seen in the kidneys, spleen and sometimes the liver but is usually asymptomatic in the latter two sites. The majority of patients have an excellent outcome on dialysis and the limited experience with renal transplantation is reasonably encouraging. However, like TTR, fibrinogen is synthesized only in the liver and hepatic transplantation is potentially curative but associated with considerable early mortality and whether long-term graft survival is better in the dual transplant group has yet to be proven.

**Generic therapies for amyloidosis**

Improved understanding of the protein-folding mechanisms underlying amyloid fibrillogenesis, and the recognition that relative instability of the precursor molecules is a key factor in amyloidogenesis, strongly support therapeutic strategies based on inhibition of fibrillogenesis. Many groups and companies are active in this area, exploring small molecules, peptides and glycosaminoglycan analogues that bind to fibril precursors and stabilize their native fold, or interfere with refolding and/or aggregation into the cross-β core structure common to amyloid fibrils, or bind to mature amyloid fibrils and promote their refolding back towards the native conformation.
Clinical studies have been completed in AA-amyloidosis using eprodisate, a glycosaminoglycan mimetic, and tafamidis in TTR amyloidosis. Both reported encouraging results without achieving their primary end-points and as yet there are no licensed agents. Other therapeutic options being explored include SAP depletion, immunotherapy and inhibitory RNAs offering real promise that specific anti-amyloid therapies may become available within the next few years.

References

REFERENCES


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Chapter 20

Primary amyloidosis (AL)

Robert A. Kyle

Although amyloid appears homogeneous and amorphous under the light microscope, it actually consists of rigid, linear, non-branching, aggregated fibrils 7.5–10 nm wide and of indefinite length. The unique staining and optical features are due to arrangement of the fibrils in an anti-parallel or cross $\beta$-pleated sheet configuration. Congo red is considered the most specific stain, which when viewed with a polarized light source, produces apple-green birefringence. Electron microscopy reveals a fibrillar pattern. The amyloid fibrils, which are deposited extracellularly generally resist proteolytic digestion. This leads to loss of normal tissue elements and ultimately organ failure. Excellent reviews of amyloidosis have been published.1,2*

All types of amyloidosis appear the same with Congo red staining and upon electron microscopy. However, the fibrils in primary amyloidosis (AL) consist of the variable portion of a monoclonal light chain (kappa or lambda); secondary amyloidosis (AA) fibrils consist of protein A, a non-immunoglobulin; familial amyloidosis fibrils are usually composed of mutated transthyretin (prealbumin); senile systemic amyloid fibrils consist of normal transthyretin and amyloid associated with long-term dialysis consists of $\beta$-2-microglobulin ($\beta_2$-M) (Table 20.1). The remainder of this chapter will be limited to primary amyloidosis.

Clinical features

The incidence of AL is 0.9 per 100,000/year. AL accounts for 79% of our amyloid practice (Fig. 20.1). The median age is 65 years, with only 1% younger than age 40 at diagnosis. Weakness, fatigue and loss of weight are the most common symptoms. The median weight loss is over 10 kg; some patients lose 20–25 kg without apparent cause. Purpura, particularly in the periorbital and facial areas, is present in one-sixth of patients. Occasionally, amyloid involvement of the hands mimics seronegative rheumatoid arthritis. Deposits of amyloid in periarticular areas of the shoulders may produce pain, swelling and prominence (shoulder pad sign). Extensive deposits of amyloid may produce pseudohypertrophy of skeletal muscles. Dyspnœa, pedal oedema, paraesthesias, light-headedness and syncope may be troublesome. Impotence may occur. Hoarseness or weakness of the voice may be a prominent feature.

The liver is palpable at diagnosis in one-quarter of patients whereas splenomegaly is present initially in only 5%. MacroGLOSSia occurs in about 10%. Generalized lymphadenopathy is infrequent. The skin is fragile and easily traumatized. Oedema from nephrotic syndrome or congestive heart failure is common. Paraesthesias and jaw or hip claudication
may be distressing. Signs and symptoms of nephrotic syndrome, renal failure, congestive heart failure, peripheral neuropathy, carpal tunnel syndrome and orthostatic hypotension must be sought during the history and physical examination.

Nephrotic syndrome or renal insufficiency is the presenting symptom in more than one-quarter of patients whereas carpal tunnel syndrome occurs in one-fifth. Congestive heart failure is the major feature at diagnosis in one-sixth of patients whereas peripheral neuropathy is present as the major manifestation in about 15%.

### Laboratory features

Anaemia is not a prominent feature unless the patient has renal failure, multiple myeloma or gastrointestinal bleeding. Thrombocytosis occurs in 10% of patients. Renal insufficiency is found in almost one-half at diagnosis and the serum creatinine is >2 mg/dl in 20%.3**

The serum protein electrophoretic pattern shows a localized band or spike in one-half but the size of the M-protein is modest (median 1.4 g/dl). Immunofixation of the

### Table 20.1 Systemic amyloidosis: immunohistochemical identification

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*AA, secondary amyloidosis; AD, haemodialysis-associated amyloidosis; AF, familial amyloidosis; AL, immunoglobulin light chain amyloidosis; FMF, familial Mediterranean fever; SSA, senile systemic amyloidosis.*

![Fig. 20.1 Amyloidosis. Mayo Clinic, 2010, n=241.](image)
serum shows a monoclonal protein in 70%. Approximately 25% have only free monoclonal light chains (Bence Jones proteinemia). Lambda light chains are twice as common as kappa. Immunofixation of the serum and urine reveals a monoclonal protein in almost 90% of patients.

About a fifth of patients have bone marrow plasmacytosis of 20% or more but the median value is only 7%. The electrocardiogram shows low voltage or loss of typical anterior septal forces mimicking the findings of myocardial infarction. The electrocardiogram is abnormal in two-thirds of patients at diagnosis. The major features are increased thickness of the ventricular walls, abnormal myocardial texture, atrial enlargement, valvular thickening and regurgitation, pericardial effusion, and abnormal diastolic function. Ultimately, reduced systolic ventricular function occurs.

Renal involvement

Nephrotic syndrome or renal failure was present in 30% of 474 patients at diagnosis. Many patients present with nephrotic-range proteinuria, hypercholesterolaemia and oedema but with a normal creatinine level. Hypoalbuminaemia is common and results in low serum oncotic pressure with loss of fluid from the intravascular space into the extravascular space producing oedema. The extent of amyloid deposits in the kidney biopsy specimen correlates poorly with the degree of proteinuria. Although the earlier literature suggests that the kidneys are enlarged in amyloid, most patients have normalized-sized kidneys by ultrasonography. The adult Fanconi syndrome, renal vein thrombosis, retroperitoneal fibrosis and priapism have been reported but are uncommon.

Diagnosis

The possibility of AL must be considered in every patient who has an M-protein in the serum or urine and who also has an unexplained nephrotic syndrome, renal insufficiency, congestive heart failure, sensorimotor peripheral neuropathy, carpal tunnel syndrome, hepatomegaly or malabsorption. In fact the presence of a monoclonal light chain in the urine of a patient with nephrotic syndrome is almost always due to AL or light-chain deposition disease.

The diagnosis requires the demonstration of amyloid deposits. Congo red staining of tissue produces an apple-green birefringence under polarized light. The use of antisera to kappa, lambda, protein A, transthyretin and β2-M is most commonly used for diagnosis.

We use a sensitive novel test for the typing of amyloidosis in clinical practice. We perform laser microdissection of Congo red staining material from specimens embedded in paraffin and then subject the specimen to tandem mass spectrometry-based proteonaemic analysis. All 50 patients with well-characterized amyloidosis were correctly identified. The increased uptake of 99mTc-pyrophosphate, thallium 201, gallium 67 and technetium-labelled aprotinin are not reliable diagnostic approaches.

An abdominal fat aspirate is positive in 70% of patients. The specimen must be stained properly with Congo red and interpreted by an experienced pathologist. Extraction of amyloid from the abdominal fat biopsy may be utilized for chemical characteristics of the amyloid type. A bone marrow aspirate and biopsy should be
performed initially to determine the number of plasma cells and document whether they are monoclonal. The bone marrow biopsy is positive for amyloid in 55% of patients. Almost 90% of patients with AL will have a positive result with subcutaneous fat biopsy or bone marrow. If these tissues are negative, rectal biopsy including the submucosa may be done. If these sites are negative and the physician is still suspicious of amyloidosis, tissue should be obtained from a suspected organ. Biopsy of the kidney, liver, sural nerve, carpal ligament, endomyocardium or small intestine are all associated with a high percentage of positivity.

*I123-labelled serum amyloid P component (I123-SAP) scintigraphy can be used for identifying and monitoring the extent of systemic amyloidosis, but it is not readily available.*

The differential diagnosis includes immunotactoid glomerulopathy. In this condition the width of the fibrils is twice that found in AL. Furthermore, extrarenal disease never develops and the deposits are not Congo red positive. Proteinuria is common but no M-protein is found. Light-chain deposition disease is characterized by the presence of non-amyloid light chains, which appear under electron microscopy as granules in the kidney. It can produce nephrotic syndrome and renal insufficiency. Occasionally, the heart and liver may be involved from the light chain deposits.

**Prognosis**

Survival in AL amyloidosis is short. In a series of 474 patients with AL within 1 month of diagnosis, the median duration of survival was 13.2 months. Those presenting with congestive heart failure had a median survival of 4 months. Death was attributed to cardiac involvement and congestive heart failure or arrhythmias in almost one-half of patients who had died. Elevated levels of NT-proBNP (N-terminal pro-brain natriuretic peptide) as well as cardiac troponins (T&I), provide important prognostic information. A study of 261 patients with newly diagnosed AL reported a survival of 6 months in patients with a detectable level of cardiac troponin T compared with 22 months for those who did not. A prognostic model consisting of NT-proBNP >332 mg/l, cardiac troponin T >0.035 μg/l, or cardiac troponin I >0.10 μg/l were classified as stages I, II or III, depending on whether none, one or both NT-proBNP and either 1 of the 2 cardiac troponins were above these levels. The survivals for stages I, II and III were 26, 10 and 3.5 months respectively. The addition of uric acid levels improve this prognostic model.

**Therapy**

Because amyloid fibrils consist of monoclonal immunoglobulin light chains, treatment with alkylating agents, which are effective against plasma cell neoplasms, has been the major approach. Results of a randomized, placebo controlled, double-blind study of 55 patients with primary systemic amyloidosis suggested that treatment with melphalan and prednisone was of some benefit. In a prospective randomized study of 220 patients conducted at our institution, patients were randomized to receive: 1) colchicine, melphalan and prednisone, 2) melphalan and prednisone or 3) colchicine alone. Patients were stratified according to their major clinical manifestation, age and sex. The median duration of survival was 8.5 months for the colchicine-treated group,
18 months for the melphalan and prednisone group, and 17 months for the melphalan, prednisone and colchicine group (p<0.001). Among patients who had a reduction in serum or urine monoclonal protein at 12 months, the overall length of survival was 50 months, whereas among those without a reduction at 12 months, the overall length of survival was 36 months (p=0.03). Thirty-four patients (15%) survived for 5 years or longer.

Measurement of organ response includes improvement in renal function as demonstrated by a 50% decrease in 24-hour urine protein excretion (mainly albumin) in the absence of a 25% increase of the serum creatinine level (minimum creatinine 0.5 mg/dl) or a 25% decrease in creatinine or iothalamate clearance. The reduction in urinary protein loss must be >0.5 g/24 hours. Liver response consists of a reduction in the size of the liver documented by radiographic or radionucleotide imaging of at least 2 cm and a decrease in the serum alkaline phosphatase of 50%. A cardiac response consists of a mean interventricular septal thickness decrease of 2 mm, 20% improvement in ejection fraction or improvement by two New York Heart Association classes without an increase in diuretic use and no increase in wall thickness. A complete haematological response requires a negative immunofixation of serum and urine, a normal free light chain ratio and fewer than 5% monoclonal bone marrow plasma cells. A partial response consists of a 50% reduction in the serum M component. The reduction must be >0.5 g/dl; a 50% reduction of light chain in the urine with a visible peak and >100 mg excretion daily and a 50% reduction of the involved free light chain, which must be >100 mg/L.

Melphalan (0.22 mg/kg) days 1–4 every 28 days plus dexamethasone 40 mg orally on days 1–4 every 28 days, produced a complete response in 33% and an overall response in 67% of patients after a median of four treatment courses. Seventy-one per cent of the 31 patients with a monoclonal protein decrease of ≥50% achieved organ improvement. At 5 years’ follow-up, the median overall survival was 5.1 years.

Treatment with alkylating agents may be associated with a myelodysplastic syndrome or acute leukaemia. Because of the improving survival of amyloidosis, the number of patients at risk for developing myelodysplasia has been increasing, with an actuarial risk at 20% at 10 years.

Thalidomide as a single agent has been disappointing for treatment of AL because it is poorly tolerated and the results have not been impressive. A combination of cyclophosphamide 500 mg orally weekly, thalidomide 100 mg daily with increase to 200 mg daily if tolerated, and dexamethasone 40 mg orally days 1–4 and 9–12 of each 21-day cycle produced a complete haematological response in 21% and an organ response in 31% of the 48 haematological responders. The estimated 3-year survival for those achieving a complete response, partial response or no response were 100%, 82% and 0% respectively. The median survival was 17 months.

Bortezomib with or without dexamethasone produced a complete response in 20% and an overall response in 68% of 76 previously treated patients with AL. The major side effects were peripheral sensorimotor neuropathy, orthostatic hypotension, peripheral oedema and constipation or diarrhoea. Bortezomib 1.6 mg/m² once weekly or 1.3 mg/m² once weekly in 31 patients with relapsed/refractory AL produced haematological responses in 50% of 30 evaluable patients.
Lenalidomide 25 mg/day for 21 days of a 28-day cycle with or without dexamethasone produced response rates of approximately 70%.\textsuperscript{20,21} It was pointed out that a dosage of lenalidomide 15 mg daily was better tolerated.

The use of dose-intensive melphalan (200 mg/m\textsuperscript{2}) followed by a peripheral blood stem cell transplant is useful for carefully selected patients. The eligibility requirements consist of biopsy-proven AL, symptomatic disease, absence of multiple myeloma, physiological age \(\leq\) 70 years, serum direct bilirubin \(\leq\) 2.0 mg/dl, reasonable performance status, lack of major co-morbidities and fewer than three organs involved, as well as absence of cardiac amyloidosis.\textsuperscript{22+}

A highly selected group of 312 patients from a total of 701 AL patients were treated with high-dose melphalan (100–200 mg/m\textsuperscript{2}) followed by autologous stem cell transplantation. A complete haematological response was achieved in 40%, and the median survival was 4.6 years for the transplanted patients. The 100-day transplant-related mortality was 13%. The median survival of the 307 patients considered ineligible for transplantation was only 4 months.\textsuperscript{23+}

In a multi-centre series of 107 patients from 48 transplant centres, the 30-day treatment-related mortality was 18%, whereas the median progression-free survival was 4 years.\textsuperscript{24} In a series from Mayo Clinic, two-thirds of patients received melphalan 200 mg/m\textsuperscript{2}. The overall treatment-related mortality was 11%. The complete response rate was 33%. Predictors of outcome included the number of organ systems involved and the baseline free light chain (FLC) value. Responders had a markedly better survival than those who did not.\textsuperscript{25}

On the other hand, in a randomized trial of 100 patients, the median survival was 57 months with melphalan plus high-dose dexamethasone compared with 49 months to those receiving a transplant. The haematological response in those who had transplants was 65%, compared with 64% of those who did not. The transplant-related mortality was 24%.\textsuperscript{26}

**General treatment measures**

The nephrotic syndrome should be treated with salt restriction and diuretics as needed. Furosemide is usually satisfactory but occasionally the addition of metolazone is helpful. Albumin infusions are not useful for long-term treatment of oedema because they are of only transient benefit and are very expensive. Diuretic therapy can produce volume contraction and a decrease in cardiac output as well as orthostatic syncope.

Long-term dialysis is necessary when azotaemia develops. Hypotension may be a problem with haemodialysis and the rapid fluid shifts can be intolerable for patients with associated congestive heart failure. Long-term ambulatory peritoneal dialysis may be useful in this setting. Neither type of dialysis is superior to the other. The median duration of survival for patients who begin dialysis is less than 1 year. The most common cause of death is cardiac rather than renal failure.\textsuperscript{27} Renal transplantation has been beneficial in a number of patients but there is a serious shortage of organ donors. Amyloid will often deposit in the transplanted kidney. Rarely, bilateral embolization of the renal artery has been performed for therapy-resistant nephrotic syndrome.
The management of cardiac amyloidosis is mainly with diuretics such as furosemide. Diuretic therapy is frequently limited by hypotension, low ejection fraction or autonomic insufficiency. Patients with cardiac amyloidosis may be very sensitive to calcium channel blockers and, consequently, these agents should be avoided. Digoxin should be limited to the control of supraventricular tachycardias or arrhythmias but not for congestive heart failure. A pacemaker is required for symptomatic bradyarrhythmias.

Sensorimotor peripheral neuropathy does not generally benefit from alkylating agent therapy. The neurological symptoms and findings usually continue to worsen in most patients. Dysethesias tend to disappear as the sensory involvement worsens. Analgesics and sedatives may be needed, depending on kind and severity of symptoms. Amitriptyline and fluphenazine have been helpful for some patients. The dysethesias may be sufficiently distressing to require narcotics for control. Codeine is useful and the long-term risks of habituation and tolerance are modest.

Treatment of orthostatic hypotension is challenging. Patients should rise slowly and sit on the edge of the bed for a few minutes before assuming an upright position. Elastic support extending to the waist (leotards) may be of some help. Fludrocortisone is often associated with increased fluid retention. Midodrine or L-THREO-3, 4-dihydroxyphenylserine (L-THREO-DOPS) may be of some benefit. Octreotide may be of help in the management of both autonomic-induced diarrhoea and orthostatic hypotension. Decompression of the carpal ligament relieves the pain of carpal tunnel syndrome but residual sensory loss is frequent.

Patients with macroglossia frequently have obstructive sleep apnoea, and this may be treated with nasal continuous positive airway pressure. Airway obstruction can be managed by permanent tracheostomy. Resection of the tongue is not advised because of bleeding. Furthermore, the remaining tongue frequently enlarges following surgery. Gastrointestinal bleeding or perforation may occur. Patients with intestinal pseudo-obstruction must not be treated surgically because resection does not relieve the obstructive symptoms and complications are common.

**Take home points**

1. Must determine the type of amyloid protein by immunohistochemistry or mass spectrometry.
2. A monoclonal (M) protein is present in serum in 70% of patients at diagnosis and in almost 90% if both serum and urine are evaluated.
3. Nephrotic syndrome or renal failure is the presenting feature in 30% of AL patients.
4. Other major features at presentation are congestive heart failure (20%), carpal tunnel syndrome (20%), peripheral neuropathy (15%) or orthostatic hypotension (10%).
5. Biopsy of subcutaneous fat and bone marrow are positive in almost 90% of AL patients.
6. Autologous stem cell transplantation is feasible in approximately 20%. Cardiac involvement manifested by troponin T $\geq$ 0.06 mg/ml, performance status $\leq$ 2 or significant involvement of $>2$ organs are contraindications for autologous transplantation.
7. Major chemotherapy regimens include melphalan and dexamethasone or bortezomib and dexamethasone.

8. A useful prognostic model utilizes NT-proBNP > 332 mg/l, troponin T > 0.035 μg/l and troponin I > 0.10 μg/l.

References

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest


   *Use of melphalan and dexamethasone for therapy.

   *Risk of myelodysplasia or acute leukaemia in melphalan-treated patients.

   *Review of thalidomide, cyclophosphamide and dexamethasone for treatment of AL amyloidosis.


   *Patients eligible for an autologous stem cell transplant have a favorable survival even when treated with chemotherapy.

   *Autologous stem cell transplantation for AL.


Chapter 21

Light-chain and heavy-chain deposition diseases

Pierre Ronco and Pierre Aucouturier

Definition

It has been known from the late 1950s that non-amyloidotic forms of glomerular disease ‘resembling the lesion of diabetic glomerulosclerosis’ could occur in multiple myeloma. The presence of monoclonal light chains (LC) in these lesions was recognized in 1973 by Antonovych et al., and confirmed in 1976 by Randall and associates¹ who published the first description of light-chain deposition disease (LCDD).

Monoclonal heavy chains were found together with light chains in the tissue deposits from some patients, thus defining light- and heavy-chain deposition disease (LHCDD). More recently, deposits containing monoclonal heavy chains only were observed in patients affected with otherwise typical Randall’s disease;² they define heavy-chain deposition disease (HCDD), which must be differentiated from the classical heavy-chain disease, a lymphoproliferative disorder in which renal involvement has infrequently been reported.

In clinical and pathological terms, LCDD, LHCDD and HCDD are basically similar, and are therefore also referred to as monoclonal immunoglobulin deposition disease (MIDD). They differ from amyloidosis by the lack of affinity for Congo red and of fibrillar ultrastructure of the deposits.

Epidemiology

MIDD occurs in a wide range of ages (26–94 years) with a slight male preponderance. It was found in 5% of myeloma patients at autopsy, whereas the prevalence of AL-amyloidosis was about 11%.³ However, myeloma accounts for only 45% of LCDD, but as in amyloidosis, monoclonal plasma cell proliferation can be demonstrated in virtually all patients by immunofluorescence examination of the bone marrow. About 30 cases of HCDD have been published so far, but it is likely that diagnosis of HCDD is markedly underestimated.

Pathogenesis

MIDD is characterized by kidney deposition of monoclonal immunoglobulin components, mostly κ light chains, but at variance with amyloidosis, deposition induces a dramatic accumulation of extracellular matrix. That light-chain deposition involves
unusual light-chain properties is supported by the absence of monoclonal free light 
chain detectable by conventional techniques in the serum and the urine in 15–30% of 
LCDD patients, the recurrence of the disease in the transplanted kidney, the biosyn-
thesis of abnormal (short or apparently large) light chains by bone marrow plasma 
cells,⁴ and the fact that discrete changes in the variable region (VL) sequence are 
responsible for light-chain deposition in a mouse experimental model. However, 
light-chain deposition does not mean pathogenicity as after mouse injection, one-third 
(14/40) of light chains from patients with myeloma or AL-amyloidosis become deposited 
in basement membranes.⁵ Thus, singular properties of light chains are most likely 
required for completion of the pathogenetic process leading to kidney fibrosis.

The following properties of monoclonal light chain may contribute to MIDD patho-
genesis. The first is the preferential usage of certain variable region germline genes. 
Second, size abnormalities of light chains have been documented in nine out of 
22 patients by bone marrow biosynthesis experiments.⁶ Third, there is a tight correlation 
between the absence of detectable circulating and urinary light chains, and their glyco-
sylation, that most likely increases their propensity to precipitate in tissues. Fourth, 
unusual amino acid substitutions have been identified in primary structures of LCDD 
light chains, mostly in peptide loops corresponding to complementarity-determining 
regions (CDRs), i.e. parts of the molecules normally implicated in antigen binding.

In the 13 HCDD patients in whom antibody mapping of the heavy chain was per-
formed, a deletion of the first constant domain CH1 was observed and associated in 
two cases with a larger deletion involving the hinge region and the CH2 (unpublished 
results and ⁷,⁸). In the blood, the deleted heavy chain was associated with light chains, 
mostly of the λ isotype, or circulated in small amounts as a free unassembled subunit. The 
CH1 deletion likely facilitates the secretion of free unassembled or partially assembled 
heavy chains that are rapidly cleared from the circulation by organ deposition. In 
addition, sequence analysis of two HCDD proteins showed unusual residues in CDR 
and framework regions of the VH.⁹ Conformational singularities of the VH probably 
contribute to heavy-chain deposition and are also most likely responsible for the 
granular aspect or fibrillar organization of the deposits found in HCDD and the rare 
patients with heavy-chain amyloidosis, respectively.

Another common feature shared by LCDD and HCDD is the dramatic accumulation 
of a qualitatively normal extracellular matrix. LCDD LCs seem to activate platelet-
derived growth factor (PDGF)-β production, resulting in mesangial cell proliferation, 
followed by transforming growth factor (TGF)-β secretion, leading to an increase in 
extracellular matrix production and a negative feedback loop inhibiting cellular pro-
liferation. Tenascin-C and LCDD LC co-localize in the centre of mesangial nodules, 
leading to nodular glomerulosclerosis.¹⁰

Pathology

Light microscopy

In virtually all patients with MIDD, tubular lesions are characterized by the deposition 
of a refractile, eosinophilic, periodic acid-Schiff (PAS)-positive, ribbon-like material 
along the outer part of the tubular basement membrane. The deposits predominate
around the distal tubules, loops of Henle, and, in some instances, around the collecting ducts. The epithelia of involved tubules are flattened and atrophied. In advanced stages, a marked interstitial fibrosis including refractile deposits is frequently associated with tubular lesions.

Glomerular lesions are more heterogeneous; nodular glomerulosclerosis resembling diabetic glomerulosclerosis is the most characteristic (Fig. 21.1a), but it is found in only two-thirds of LCDD patients. Nodules are composed of membrane-like material with nuclei at the periphery. The capillary loops stretch at the periphery of florid nodules and may undergo aneurysmal dilatation. Milder glomerular forms simply show an increase in mesangial matrix and sometimes in mesangial cells, and a modest thickening of the basement membranes. Glomerular lesions may also not be detected by light microscopy but require ultrastructural examination. Arteries, arterioles and peritubular capillaries all may contain deposits in close contact with their basement membranes.

**Immunofluorescence**

A key step in the diagnosis of the various forms of MIDD is immunofluorescence examination of biopsy specimens, which all show evidence of monotypic light- (Fig. 21.1b) and/or heavy-chain (Fig. 21.2) fixation along basement membranes. These criteria are mandatory for the diagnosis of MIDD. In contrast with AL-amyloidosis, the κ isotype

![Fig. 21.1](image)

_Fig. 21.1_ Light-chain deposition disease. (a) Nodular glomerulosclerosis with mesangial matrix accumulation (Masson trichrome staining, 312). (b) Bright staining of mesangial nodules and tubular basement membranes with anti-κ antibody (immunofluorescence, 125), (Béatrice Mougenot’s personal collection).
is more frequent and detected in about 80% of patients with LCDD. In addition, examination with anti-heavy-chain antisera of biopsy specimens that did not stain for light chain has permitted both the identification of HCDD as a separate entity and the demonstration of heavy chain C-domain deletions (Fig. 21.2). The tubular deposits stain strongly (Fig. 21.1b) and predominate along the loops of Henle and the distal tubules. In contrast, the pattern of glomerular immunofluorescence displays marked heterogeneity. In patients with nodular glomerulosclerosis, deposits of monotypic immunoglobulin chains are usually found along the peripheral glomerular basement membranes and to a lesser extent in the nodules themselves (Fig. 21.1b). In some cases, glomerular immunofluorescence is negative despite the presence of large amounts of granular glomerular deposits as seen by electron microscopy. Deposits of immunoglobulin chains are constantly found in vascular walls.

Patients with LHCDD have not been studied extensively. A recent report shows a striking overrepresentation of the IgG3 subclass, and fixation of complement components C1 and C3.\textsuperscript{11}

In patients with HCDD, the $\gamma$ chain (IgG heavy chain) is by far the most frequent (~90% reported cases), whereas the $\alpha$ and $\mu$ isotypes are rare. Immunofluorescence with anti-light-chain antibodies is negative despite typical nodular glomerulosclerosis. Among $\gamma$-chain HCDD, there is a remarkable frequency of the $\gamma3$ subclass, which is

![Fig. 21.2](image-url)  
**Fig. 21.2** Heavy-chain deposition disease. Nodular glomerulosclerosis. Mesangial and parietal deposits stain with a monoclonal antibody specific for the $\gamma1$ isotype in the absence of detectable light chain (bottom right). Immunofluorescence with a panel of monoclonal antibodies directed to the various constant domains of the $\gamma$ heavy chain shows that glomerular deposits are stained with anti-CH2 and anti-CH3 but not with anti-CH1 antibodies (312), (Béatrice Mougenot’s personal collection).
very rare in monoclonal gammopathies. Of note, IgG3 HCDD cases generally feature hypocomplementaemia. In all biopsy specimens studied with monoclonal antibodies specific for \( \gamma \)-chain constant domains, the CH1 domain epitopes were undetectable (Fig. 21.2) in agreement with immunochemical analyses of the patients’ serum and urine.\(^7\),\(^12\)

**Electron microscopy**

The most characteristic ultrastructural feature is the presence of fine or coarse granular electron-dense deposits that delineate the outer aspect of the tubular basement membranes. Glomerular lesions are characterized by the deposition of a non-fibrillar electron-dense material in the mesangial nodules and along the glomerular basement membrane.

**Clinical manifestations**

There are a number of clinical manifestations of MIDD,\(^13\)–\(^16\), especially in LCDD that may feature deposition of immunoglobulin light chains along basement membranes of a variety of organs. Light-chain deposition in these organs may be, however, totally asymptomatic. In HCDD, extrarenal deposits have only been described in a few patients, in the liver, the thyroid follicles, the skin and the muscle.\(^2\),\(^17\) Another patient presented with seronegative rheumatoid arthritis and \( \gamma3 \)-chain deposits in synovial tissue.\(^18\)

**Renal manifestations**

Renal involvement is a constant feature of MIDD, and renal symptoms, mostly proteinuria and renal failure, often dominate the clinical presentation. In 23–53% of LCDD patients, albuminuria is associated with the nephrotic syndrome. In 20%, the albumin loss is less than 1 g/day, and these patients exhibit mainly a tubule-interstitial syndrome. Haematuria is more frequent (45%) than one would expect for a nephropathy in which cell proliferation is usually modest.

Renal failure is remarkable for its high prevalence (93%), early appearance and severity, irrespective of urinary albumin output. It may present in the form of a subacute tubule-interstitial nephritis or a rapidly progressive glomerulonephritis respectively. The prevalence of hypertension is variable and probably higher in HCDD, but it must be interpreted according to associated medical history.

**Extrarenal manifestations**

Liver and cardiac clinical involvements occur in approximately one-quarter of patients with LCDD and LHCDD.\(^13\) Liver deposits are constant. They are either discrete and confined to sinusoids and basement membranes of biliary ductules without associated parenchymal lesions, or they are massive with marked dilatation and multiple ruptures of sinusoids, resembling peliosis. Hepatomegaly and mild alterations of liver function are the most usual symptoms, but patients may also develop life-threatening hepatic insufficiency and portal hypertension.

Heart involvement may be responsible for cardiomegaly and severe heart failure. Arrhythmias, conduction disturbances and congestive heart failure are seen.
Echocardiography and catheterization may reveal diastolic dysfunction and reduction in myocardial compliance similar to that found in cardiac amyloid. As in the kidney and liver, monotypic LC deposits in the vascular walls and perivascular areas of the heart were observed in all autopsy cases.\textsuperscript{19}

Deposits also may occur along the nerve fibres and in the choroid plexus, as well as in the lymph nodes, bone marrow, spleen, pancreas, thyroid gland, submandibular glands, adrenal glands, gastrointestinal tract, abdominal vessels, lungs and skin.\textsuperscript{20} They may be responsible for peripheral neuropathy (20% of the reported cases), gastrointestinal disturbances, pulmonary nodules, amyloid-like arthropathy and sicca syndrome. In some patients, non-amyloidotic localized nodules, termed ‘aggregomas’, develop in the lung or as cervical mass without systemic LCDD.\textsuperscript{21}

**Haematological findings**

The most common underlying disease in MIDD is myeloma. Its incidence is significantly lower in HCDD (24%) compared with LCDD (53%), which could mean that these conditions might arise from a different set of haematological contexts. MIDD is often the presenting disease leading to the discovery of myeloma at an early stage. Some patients who presented with common myeloma and with normal-sized monoclonal immunoglobulin in the absence of kidney disease developed LCDD and immunoglobulin structural abnormalities when the myeloma relapsed after chemotherapy.\textsuperscript{19} Because melphalan may induce Ig gene mutations, the disease in these patients might result from the emergence of a variant clone caused by the alkylating agent.

MIDD occasionally may complicate Waldenström’s macroglobulinaemia, chronic lymphocytic leukaemia and nodal marginal zone lymphoma. It often occurs in the absence of a detectable malignant process, even after prolonged (more than 10 years) follow-up. In such ‘primary’ forms, a monoclonal bone marrow plasma cell population is easily detected by cytoplasmic immunofluorescence and bone marrow biosynthesis experiments. It is worth noting that in 15–30% of patients with LCDD, there is no detectable monoclonal immunoglobulin in the serum and urine even by sensitive techniques including immunofixation, although an immunoglobulin light chain is deposited in those patients’ tissues. Even a sensitive free light-chain assay fails to detect the circulating free light chain in about 10% of cases.

Among 27 patients with HCDD, only six had a myeloma and 12 had no detectable monoclonal component in the serum and in the urine, which suggests that these γ chains were rapidly cleared from the circulation (review in\textsuperscript{22}).

**Outcome and treatment**

The outcome of MIDD remains uncertain, mainly because extrarenal deposits of LC can be totally asymptomatic or cause severe organ damage that leads to death. Survival from onset of symptoms varies from 1 month to 10 years. In the largest series,\textsuperscript{23} 57% of the patients reached uraemia and 59% died during follow-up (mean 27.5 months), and patient survival was only 66% at 1 year and 31% at 8 years, although 86% of the patients received chemotherapy. The only variables that were independently associated with renal survival were age and degree of renal insufficiency at presentation or the
time of renal biopsy. Variables that were independently associated with a worse patient survival were age, initial creatinine, associated multiple myeloma and extrarenal LC deposition. Survival of the uraemic patients who were treated with dialysis was not different from that of the patients who did not reach uraemia.

As in AL-amyloidosis, treatment should be aimed at reducing Ig production. Clearance of the LC deposits has been demonstrated unequivocally in a few patients after intensive chemotherapy with syngeneic bone marrow transplantation or blood stem cell autografting. Disappearance of nodular mesangial lesions and LC deposits was also reported after long-term chemotherapy. These observations demonstrate that fibrotic nodular glomerular lesions are reversible, and they argue for intensive chemotherapy in patients with severe visceral involvement.

In a retrospective study of 11 patients (<65 years) who had L(H)CDD and were treated by high-dosage therapy with the support of autologous blood stem cell transplantation, no treatment-related death occurred. A decrease in the monoclonal Ig level was observed in eight patients, with complete disappearance from serum and urine in six cases. Improvement in manifestations related to deposits was observed in six patients, and histological regression was documented in cardiac, hepatic and skin biopsies. No manifestation related to deposits occurred or recurred in any patient. These results were confirmed in three small North American series. Reversal of dialysis dependence and sustained improvement of renal function were noted also in one patient with LCDD.

Whether high-dosage chemotherapy with blood stem cell transplantation provides benefits compared with conventional chemotherapy, including high-dosage dexamethasone, remains to be established. The former should be preferred in patients with LCDD and overt myeloma, whereas the latter is the only therapy for those who are older than 65 years. Because the new proteasome inhibitors (Velcade®) and thalidomide derivatives have shown great efficacy in myeloma patients and AL-amyloidosis, their use may profoundly change the therapeutic protocols in patients with light-chain and heavy-chain deposition diseases.

As in AL-amyloidosis, monitoring of LC production should rely on serum free LC assay, particularly in patients without a blood and urine monoclonal component. Kidney transplantation has been performed in a few patients with MIDD. Usually, recurrence of the disease is observed. Therefore, kidney transplantation should not be an option for patients with LCDD unless measures have been taken to reduce LC production.

### Renal diseases associated with MIDD

Amyloid deposits are found in one or more organs in about 7% of LCDD patients. Because amyloid deposits are focal, the true incidence of the association may be markedly underestimated. It is generally considered that myeloma cast nephropathy and MIDD occur in mutually exclusive fashion. In fact, a few myeloma casts are identified in about 30% of patients with MIDD. Conversely, in typical cast nephropathy, light-chain deposits are not infrequent along glomerular and tubular basement membranes; however, these do not usually show the ribbon-like thickening characteristic of MIDD. Whether these light-chain deposits correspond to an early stage of MIDD cannot be established yet.
**Take-home points**

1. The diagnosis of MIDD must be suspected in any patient with the nephrotic syndrome or rapidly progressive tubule-interstitial nephritis or with echocardiographic findings indicating diastolic dysfunction and the presence of a monoclonal Ig component in the serum and/or the urine. The same combination is seen also in AL-amyloidosis, which is more often associated with the λLC isotype, whereas LCDD is associated with the κLC isotype.

2. Renal biopsy plays an essential role in the diagnosis of MIDD and of the associated dysproteinaemia because sensitive techniques, including immunofixation, fail to identify a monoclonal Ig component in 10–20% of patients with LCDD/LHCDD and approximately 40% of patients with HCDD. A serum free light-chain assay fails to detect circulating monoclonal light chain in about 10% of LCDD cases.

3. The definitive diagnosis is made by the immunohistological analysis of tissue from an affected organ, in most cases the kidney, using a panel of Ig chain-specific antibodies, including anti-κ and anti-λ LC antibodies to stain the non-Congophilic deposits.

4. When the biopsy stains for a single HC isotype and does not stain for LC isotypes, the diagnosis of HCDD should be suspected, and the monoclonality of the deposits should be confirmed with anti-γ heavy-chain subclass antibodies.

5. The diagnosis of the plasma cell dyscrasia relies on bone marrow aspiration and biopsy with cell morphological evaluation and, if necessary, immunophenotyping with anti-κ and anti-λ antisera to demonstrate monoclonality.

6. The respective indications of high-dose chemotherapy with blood stem cell autografting and conventional chemotherapies are rapidly evolving because of the efficacy of proteasome inhibitors and thalidomide derivatives in myeloma patients.

**References**

Papers of particular interest have been highlighted as:

* of special interest

** of outstanding interest


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Chapter 22

Hepatitis C virus-associated mixed cryoglobulinaemia

Edgar D. Charles

Introduction

Hepatitis C virus (HCV) chronically infects over 170 million people worldwide and is the leading indication for liver transplantation in the USA and Europe. HCV is a positive strand RNA virus with a 9.6 kb genome that replicates predominantly in the liver. HCV frequently causes extrahepatic manifestations, the most common and severe of which is mixed cryoglobulinaemia (MC), characterized by the reversible precipitation of immune complexes containing rheumatoid factor (RF) (which is usually IgMκ RF), polyclonal IgG, HCV RNA and complement. These immune complexes deposit on endothelial surfaces of small and medium sized arteries and veins, leading to vascular inflammation. Vessels in the skin, kidneys and peripheral nerves are most frequently affected, variably leading to clinical manifestations of palpable purpura, glomerulonephritis (GN) and neuropathy. It is clear that HCV MC is caused by the aberrant activation and proliferation of autoreactive B cells. However, it remains unknown what triggers these B cells to activate, clonally expand and differentiate to produce pathological quantities of self-reactive RF during chronic HCV infection.

Classification and serological detection of cryoglobulinaemia

Meltzer originally described clinical MC in 1966 as a triad of palpable purpura, arthralgia and asthaenia accompanied by organ involvement (e.g. nephropathy and neuropathy) and elevated serum RF, defined as immunoglobulin (Ig) capable of binding IgG.¹ This triad is now known to be rare; many MC patients are asymptomatic, and the most common clinical manifestation is palpable purpura, which is often transient. Cryoglobulins are classified as type I (monoclonal Ig only), type II (mixture of monoclonal Ig, which is usually IgM RF, and polyclonal IgG) and type III (mixture of polyclonal Ig, which is usually IgM, and polyclonal IgG).² ‘Essential’ MC refers to the subset of MC patients for whom no cause has been identified; since the identification of HCV in 1989, it has been recognized as the cause of >90% of MC, and <5% of cases are now considered ‘essential’.³⁻⁵ HCV is primarily associated with type II MC (which typically has an IgMκ RF with anti-idiotypic activity⁶), and to a lesser extent, with type III MC. Type I MC is rarely seen in HCV. Apart from HCV, other causes of MC include infectious agents (e.g. human immunodeficiency virus (HIV), hepatitis B virus (HBV))
HEPATITIS C VIRUS-ASSOCIATED MIXED CRYOGLOBULINAEMIA

and autoimmune disorders (e.g. systemic lupus erythematosus (SLE), Sjögren’s syndrome and systemic sclerosis). A common feature of these disorders is chronic inflammation in the setting of high antigenic load, suggesting that antigen-driven B cell dysregulation underlies the development of clinically apparent MC.

Serological testing for cryoglobulins is straightforward, but serum preparation must be performed at 37°C to prevent premature immune complex precipitation and false negative results. Serum is stored at 4°C for 7 days and inspected daily for a precipitate. The cryocrit, the percentage of cryoglobulin in the serum, is calculated by spinning the serum in a Wintrobe tube. A cryocrit ≥2% is considered to be positive. The cryocrit may then typed using immunofixation. Some chronic HCV patients with MC may be HCV Ab+ yet have undetectable plasma HCV RNA. In such cases, examination of the cryocrit for HCV RNA is warranted.

The HCV lifecycle

HCV is an enveloped positive strand RNA virus in the genus Hepacivirus and the family Flaviviridae. The 9.6 kb RNA genome contains large 5’ and 3’ non-coding regions (NCR) that are essential to translation and replication. Entry into the cell is dependent on interaction with a defined array of entry factors (CD81, scavenger receptor-B1, claudin-1 and occludin); this array plays a major role in species and tissue tropism. HCV translation and replication occur in association with a membranous web believed to derive from the endoplasmic reticulum. Translation of the single, long open reading frame yields a polyprotein of approximately 3000 amino acids. This polyprotein is cleaved by host and viral proteases to release the ten individual proteins that comprise the viral particle and replication machinery. Core, E1, E2 and p7 proteins are structural proteins in the N-terminal third of the polyprotein. Downstream of these are the non-structural proteins, NS2, NS3, NS4A, NS4B, NS5A and NS5B, which have enzymatic functions. HCV replication is likely to follow the strategy used by other positive-strand RNA viruses. The 3’ NCR is likely to have an important function in initiating genome replication. The viral genome is transcribed in the cytoplasm to yield a complementary negative-strand RNA that serves as a template for positive-strand RNA molecules. HCV has no reverse-transcriptase activity; NS5B, an error-prone RNA-dependent RNA polymerase lacking proofreading capacity, synthesizes both negative and positive strand RNA. The 5’ NCR contains an internal ribosome entry site that allows cap-independent translation of viral RNA. Infectious particles are thought to comprise HCV RNA associated with the structural proteins core, E1 and E2 and surrounded by a lipid envelope. The non-structural proteins are not likely to be present in viral particles. After assembly, viral particles leave the cell, most likely by the constitutive secretory pathway.

The major site of HCV replication is the liver, but the high rate of extrahepatic manifestations during chronic HCV infection have led some to suggest that other tissues may also be infected. Other cell types reported to contain HCV RNA include B cells, dendritic cells, monocytes, and gut mucosal and sperm cells. It has been proposed that latent infection may persist in many of these cells after elimination of virus from the peripheral blood. However, the vast majority of accumulating clinical data suggests
that such an infectious reservoir, if it exists, does not pose a significant risk for either reinfection or transmission of virus.

**Epidemiology of HCV-related MC**

Estimates of MC prevalence in HCV infection vary widely, ranging from 10% to 70%; many of these differences may be due to population selection and lead time biases. Additionally, the clinical assessment of MC is not standardized, and as discussed above, the laboratory test for MC is prone to false negative results. MC is associated with increased duration of HCV infection; HCV⁺MC⁺ patients have an apparent duration of HCV infection that is almost twice as long as in HCV⁺MC⁻ patients, and an Italian HCV⁺ population was found to have a yearly incidence rate of 3%. All HCV genotypes have been found in HCV MC, and there is no clear association with a particular genotype. Female gender may predispose towards MC, although this association is not strong.

MC is more prevalent in Southern Europe than in Northern Europe and North America; up to 60% of HCV-infected individuals in Southern Europe have MC, whereas the prevalence among HCV⁺ patients in the USA (where no ethnic bias for MC has been reported) is considerably lower (10–50%). The prevalence of symptomatic MC is much lower than that of laboratory-detected MC. It is unclear whether this difference is due to unidentified genetic factors. Although genomewide association scans have not been performed, several investigators have focused on human leucocyte antigen (HLA) alleles. These studies are limited by their small sample sizes. Additionally, it is challenging to compare studies, as they use different HLA typing methods they involve different ethnic populations with dissimilar HLA frequencies. Nevertheless, several studies conducted primarily in Italy, France and China have associated DRB1*11 alleles and DR3, DR5 and DR6 serological clusters with MC. However, a group in Japan failed to detect any significant associations between HLA and HCV MC.

**Pathogenesis of HCV-induced MC**

HCV MC is caused by aberrant RF B cell lymphoproliferation. Although the total number of B cells is similar between MC patients and healthy individuals, clonal B cell expansions are present in the liver and peripheral blood of MC patients. These B cells express memory markers and are overwhelmingly biased towards the RF-encoding V_H 1–69, J_H 4 and V_k 3–20 gene segments, which are also preferentially expressed in HCV-related NHL. It is unclear why such an expansion occurs more readily in chronic HCV infection, compared with other chronic viral diseases such as HBV or HIV. Increased serum B cell-activating factor (BAFF), a tumour necrosis factor (TNF)-α family member required for B cell survival, has been reported in HCV MC, as well as in SLE, rheumatoid arthritis and Sjögren’s syndrome. BAFF inhibits B cell apoptosis, and high levels may allow the survival of autoreactive B cells. Interestingly, BAFF promoter polymorphisms may predispose to MC, but additional studies are needed to confirm this association.
It has been proposed that HCV infects B cells, leading to direct malignant transformation. However, this model fails to explain the IgV gene segment restriction seen in HCV MC, unless it is presumed that HCV preferentially infects RF B cells. Nevertheless, a B cell line that productively releases infectious HCV has been reported, and several groups have claimed to detect minus strand RNA, the HCV replicative intermediate, associated with lymphocytes from HCV+ patients; however, it has been demonstrated that artifactual detection may occur, possibly through non-specific priming events. One group has failed to detect HCV infection in malignant B cells, and it has been shown that B cells lack necessary HCV entry receptors and cannot support HCV replication, but can associate with low levels of HCV RNA. Furthermore, when HCV MC patients are treated with rituximab (a monoclonal antibody specific for CD20, which is present on mature B cells), serum HCV RNA levels often increase, arguing against a potential B cell reservoir of HCV infection. Taken together, cumulative data suggest that HCV viral particles may be bound directly or indirectly to B cells, but HCV rarely infects B cells.

It has alternatively been postulated that specific HCV proteins are necessary for clonal B cell expansion. The suggested IgG Fc binding activity of HCV core could possibly lead to enhanced HCV-immune complex generation. Also, NS5A protein may sequester p53 and predispose cells towards proliferation; however, as NS5A expression requires active replication, this scenario necessitates B cell infection. High concentrations (5 μg/ml) of HCV E2 protein in vitro polyclonally stimulate B cell expansion via interactions with CD81, a known HCV E2 entry factor. It has also been claimed that HCV E2-CD81 interactions trigger activation-induced cytidine deaminase expression resulting in stochastic immunoglobulin hypermutation. Neither of these scenarios explains the clonal RF B cell expansion seen in HCV MC patients. However, the BCR cloned from an HCV-associated NHL was shown to bind HCV E2, and it was hypothesized that simultaneous engagement of the BCR and CD81 could result in a reduced B cell stimulation threshold. Another group has reported that a minority of HCV MC patients’ IgM RF cross-reacts with IgG Fc and HCV NS3, and it has been speculated that RF activity is generated during the normal adaptive immune response to HCV. Further translational work is necessary to determine the requirements for B cell survival, stimulation and differentiation in HCV MC patients.

The abnormal expansion of RF B cells in the peripheral blood is accompanied by a commensurate increase in detectable IgMκ RF in the serum. Immune complexes of pentameric IgM RF, polyclonal IgG and HCV particles may in turn be potent proinflammatory stimuli. IgM Fc effectively binds C1q, and these Fc regions are likely to be accessible in a pentameric configuration. Binding to epithelial cells via the C1q receptor is thought to elicit vascular inflammation via the recruitment of NK cells and neutrophils; the subsequent mechanisms of inflammation remain unclear.

**Clinical manifestations of HCV-related MC**

*Cryoglobulinaemic vasculitis* HCV MC vasculitis primarily involves the small and medium sized vessels of the skin, kidneys and peripheral nerves, although almost any organ may be affected. Histology typically reveals a leucocytoclastic vasculitis, with deposition of IgMκ RF, IgG, C3 and neutrophils in the vessel wall. A necrotizing vasculitis, with
fibrinoid necrosis of the intima and the inflammation of the entire vessel wall and perivascular space, may also occur.

Signs and symptoms of systemic vasculitis correlate with the detection of circulating cryoglobulins; however, cryoglobulins may not be detected by laboratory analysis if blood samples have not been kept at 37°C until sera is isolated. If an HCV-infected patient has definite vasculitic symptoms, yet cryoglobulins are not detected, then other laboratory tests may suggest the presence of MC. Serum RF (usually IgMκ) is consistently elevated in HCV MC. Total fractions of serum IgM and IgG are often non-specifically increased, and serum protein electrophoresis may reveal a monoclonal IgMκ and polyclonal IgG gammopathy. Complement component C4 is frequently profoundly depressed, and it may be a suitable biomarker for disease activity. C1q, C3 and CH50 are frequently low, but C3 in particular does not correlate well with apparent disease activity. MC activity does not correlate well with HCV RNA, liver transaminases or liver histology.

Palpable purpura (primarily of the lower legs, although lesions can appear elsewhere), occurs in more than 90% of patients with symptomatic HCV MC, is frequently intermittent and is often the initial manifestation of HCV MC. These purpuric lesions may occasionally progress to chronic ulcers and frank gangrene. Histopathological examination reveals inflammatory infiltrates in blood vessel walls, associated with fibrinoid necrosis and haemorrhage.

Renal disease is usually type I membranoproliferative glomerulonephritis (MPGN), and it frequently heralds a poor clinical course complicated by infection and cardiovascular disease.

Renal disease is usually type I membranoproliferative glomerulonephritis (MPGN), and it frequently heralds a poor clinical course complicated by infection and cardiovascular disease. Glomerular disease commonly presents with proteinuria and microscopically haematuria, with or without kidney impairment. Patients experience a nephrotic or acute nephritic syndrome with deterioration of renal function in 20–30% of patients. However, the clinical course varies widely, with waxing and waning of extrarenal signs of systemic vasculitis that are frequently correlated with renal involvement. However, renal disease may flare in the absence of these signs and symptoms. Typically, the renal disease follows an indolent course, although in a substantial minority of patients, it progresses to end-stage renal failure requiring dialysis.

Neurological involvement has a variable incidence. Sensorimotor neuropathy may arise from cryoglobulin deposition in the vasa vasorum. Painful paraesthesias and concomitant weakness, particularly in the lower limbs may occur, as may isolated mononeuritis, manifested by foot or wrist drop.

B cell non-Hodgkin lymphoma (NHL) has been linked HCV infection. It is likely that HCV MC represents an antigen-driven, relatively benign clonal B cell lymphoproliferation that, with continued antigenic stimulation, occasionally progresses towards overt NHL. Typically, the NHL that arises in HCV MC patients is a low-grade marginal zone NHL, although associations with diverse subtypes have been reported. Clonal RF B cells have been detected in the liver, spleen, peripheral lymph nodes, peripheral blood and/or bone marrow. It has been proposed that a subset of these low-grade NHL evolve to a high-malignancy phenotype. Consistent with the hypothesis that continued antigenic presence is required for ongoing clonal B cell proliferation, eradication of HCV can lead to disappearance of the associated low-grade NHL, similar to what has been observed with Helicobacter pylori-induced mucosa-associated lymphoid tissue (MALT) lymphomas.
Histological features of cryoglobulinaemic GN

MPGN with subendothelial deposits is most frequently observed. Immunofluorescence microscopy reveals deposits of IgMκ RF, IgG and C3 on the capillary wall and mesangium. There are several features that differentiate cryoglobulinaemic GN from idiopathic type-I MPGN.

1) The glomerulus is densely infiltrated with leucocytes, primarily monocytes and macrophages.56–59

2) Intraglomerular deposits, frequently subendothelial (as in all MPGN), may also fill the capillary lumen, particularly in patients with acute nephritic syndrome. These ‘intraluminal thrombi’ are large, eosinophilic, periodic acid-Schiff (PAS)-positive intraluminal deposits that are amorphous immune complex-like deposits that may have a specific fibrillar or cylindrical structure identical to that of cryoprecipitate. These cylinders are 100–1000 μm long and have a hollow axis, with a cross-sectional appearance of annular bodies.60–62 Immunohistochemistry suggests that these deposits contain IgMκ RF.63

3) The thickening of the glomerular basement membrane, which has a double-contoured appearance, is more diffuse and visible than in lupus nephritis and in idiopathic MPGN. However, the interposition of mesangial matrix and mesangial cells between the basement membrane and the newly formed basement membrane-like material is less pronounced than in other MPGN. Electron microscopy shows that monocytes and macrophages are in this interposition and are in intimate contact with the subendothelial deposits. It has been speculated that the relatively mild mesangial involvement may explain why glomerular segmental and global sclerosis is less severe compared with other types of MPGN.64

A minority of patients with HCV and cryoglobulinaemic MPGN have renal biopsy findings suggestive of type I MPGN with centrilobular mesangial sclerosis; these findings are indistinguishable from idiopathic MPGN, except for the presence of monocyte infiltration. Approximately 20% of patients have biopsies that show mild mesangial proliferative GN with moderate or absence of monocytic infiltration. Usually these patients have mild urinary abnormalities or have received intensive immunosuppression.

About 30% of patients with cryoglobulinaemic GN have acute vasculitis of the small and medium sized renal arteries, characterized by fibrinoid necrosis of the arteriolar wall and infiltration of monocytes in and around the wall.50 This renal vasculitis can appear in the absence of glomerular involvement, and other signs of systemic vasculitis are frequently present. Even when fibrinoid necrosis of the arterial walls is severe, segmental necrosis of the capillary loops and widespread crescentic extracapillary proliferation appear to be extremely rare.50,65

Treatment

Consistent with HCV MC being an antigen-stimulated disease, the most effective treatment is eradication of the underlying HCV infection. The goal of antiviral treatment is sustained virological response (SVR), defined as clearance of HCV RNA that persists at least 6 months after completion of anti-virals. Signs and symptoms of MC
almost always disappear in patients with SVR, although persistence has been rarely described. This persistence may be reflective of continued HCV replication below the limit of detection, or long-term persistence of viral antigen in the absence of replicating virus (e.g., long-term sequestration by follicular dendritic cells). HCV RNA relapse is associated with recurrence of MC and clinical symptoms.

The current standard of care for HCV infection is pegylated interferon-α2a/2b (peg-IFN) in combination with ribavirin (RBV). Pegylated interferons are polyethylene glycol conjugates of interferon that have an increased plasma half-life allowing weekly (as opposed to thrice-weekly with standard interferon) subcutaneous injections. Two forms of peg-IFN–α, 2a (180 μg/kg/week), and 2b (1.5 μg/kg/week), appear to have similar efficacy for genotype 1-infected patients when dosed with 1000 mg/day (body weight <75 kg) or 1200 mg/day (body weight >75 kg) of RBV. Therapy with peg-IFN/RBV results in a SVR of 45–50% in genotypes 1 and 4 (which require 48 weeks of treatment), and 70–80% in genotypes 2 and 3 (which require 24 weeks of treatment) in patients with HCV monoinfection. SVR rates are substantially reduced in patients with HCV and HIV co-infection.

There is a lack of prospective, randomized controlled trials evaluating treatments for HCV MC and HCV MC-associated GN. Anti-viral therapy with an aim of SVR should be the primary goal for these patients. Small studies have shown that standard IFN (3 MU ×3/week) with RBV is effective in treating HCV in MC patients, many of whom have underlying renal involvement. Importantly, eradication of HCV with IFN/RBV leads to resolution of HCV MC-associated splenic villous lymphomas and immunocytomas. Small studies have revealed SVR rates between 53% and 78% have been achieved in HCV MC patients treated with peg-IFN/RBV; in one of these studies, GFR <70 ml/min was negatively correlated with SVR.

Treatment with anti-virals must be individualized for HCV GN patients. The doses of peg-IFN and RBV must be adjusted in patients with renal failure. RBV, which causes a dose-dependent haemolytic anaemia, is cleared by the kidneys, and it is not recommended in individuals with creatinine clearance <50 ml/min and in those undergoing dialysis. Low dose (≤200 mg/day) RBV may be considered in a well-monitored setting that includes weekly haemoglobin monitoring and mechanisms for rapid RBV discontinuation and/or recombinant erythropoetin supplementation. Moreover, peg-IFN/RBV is poorly tolerated in ESRD, even with weekly plasma monitoring, and IFN is contraindicated in renal allograft recipients, as IFN may precipitate acute graft rejection.

The treatment landscape for HCV is rapidly evolving, with anti-HCV protease inhibitors and polymerase inhibitors expected to soon reach clinical use. It appears that peg-IFN/RBV will need to be co-administered with these agents for optimal anti-viral effect. Clinical trials will be necessary to determine whether combinations of HCV-specific anti-viral medications will obviate the need for, or shorten the duration of, peg-IFN/RBV therapy in the future.

For patients unable to tolerate anti-virals, for those who have failed to reach SVR after anti-viral therapy or for those with severe renal disease, symptomatic treatment of vasculitis with immunosuppressive therapy (e.g., rituximab, oral corticosteroids and methotrexate) or plasmapheresis should be considered. However, there are insufficient clinical data to support which of these modalities is optimal for the symptomatic treatment of HCV MC.
Rituximab is a chimeric monoclonal antibody that binds to the pan B cell marker, CD20, and effects B cell destruction via complement-dependent and antibody-mediated cellular cytotoxicity. Following a standard course of 375 mg/m²/week × 4 weeks, B cells are typically undetectable in the periphery, and they take 6–18 months to recover. Several small studies have shown that 80–93% of patients with HCV MC vasculitis respond to rituximab, and the reduction of peripheral V_{H} 1–69⁺ memory B cells persists 12 months after treatment. Vasculitic symptoms usually reappear with reconstitution of peripheral B cells. Rituximab appears to be generally safe and well tolerated in HCV MC; however, data regarding its use are derived from small series or case reports without long-term follow-up. Rituximab has been associated with modestly elevated (up to twofold) levels of HCV viraemia, presumably due to reduction of partially protective humoral control. Of note, several reports of fatal fulminating hepatitis due to HBV reactivation have been observed in patients treated with rituximab. The safety and efficacy of multiple courses of rituximab in the setting of HCV MC are unknown. Studies are needed to determine the optimum duration, dosage and readministration of rituximab in HCV MC.

Corticosteroid therapy has been used to treat acute MC flares in the setting of severe GN. Current recommendations suggest intravenous methylprednisolone bolus 0.5–1 g/day for 3 consecutive days followed by oral corticosteroid 0.5 mg/kg/day slowly tapered to 0.1–0.2 mg/kg/day for 4–6 months. Alternatively, oral cyclophosphamide (1–2 mg/kg/day for 2–4 months) may be considered. However, it must be stressed that systemic immunosuppression is not curative, has significant side effects, and may lead to increases in HCV viral load.

There are extremely limited data on the palliative use of plasmapheresis (exchanges of 2–3 l plasma × 3/week for 2–3 weeks) to treat HCV MC vasculitic symptoms via removal of circulating cryoglobulins. Case reports suggest that it is safe, and may result in improvement in glomerulonephritis, neuropathy and purpura. However, given the possibility of rebound effects on discontinuation it has been recommended that corticosteroids be co-administered. Randomized controlled trials are needed to determine the appropriate use of these alternative therapies for HCV MC.

**Take home points**

1. HCV-related cryoglobulins contain RF, polyclonal IgG and HCV RNA that precipitate and deposit on vascular endothelium, causing an end-organ vasculitis predominantly in skin, kidneys and peripheral nerves.

2. Patients often have striking clonal expansions of RF-bearing memory B cells with restricted usage of RF-encoding Ig gene segments. Most of these activated B cells have low to moderate levels of somatic hypermutations that suggest an immunological response to antigenic stimulation.

3. A smaller subset of patients with MC develop a low-grade NHL comprising B cells that are immunophenotypically similar to the expanded B cells seen in MC. The antigenic dependence of these B cells is supported by evidence that HCV-related MC and NHL disappear after successful treatment of HCV infection.
4. Treatment of HCV-related MC should aim to eradicate HCV infection. MC symptoms almost always resolve within 6 months of successful virological clearance. However, patients who are unlikely to tolerate or benefit from anti-HCV therapy may be offered symptomatic therapy with immunosuppressives (e.g. rituximab, corticosteroids or cyclophosphamide) or plasmapheresis.

5. Continued patient-centred studies are necessary to elucidate the pathogenesis of HCV MC and to devise improved therapeutic strategies for affected patients.

Acknowledgments

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Hepatitis B-associated renal diseases

Kar Neng Lai and Sydney C.W. Tang

Historical perspective
Following the landmark discovery in 1965 of the Australian antigen, subsequently renamed the hepatitis B surface antigen (HBsAg), Combes and co-workers first described the occurrence of membranous nephropathy (MN) due to glomerular deposition of Australian antigen-containing immune complexes in a 53-year-old man in 1971. Different histological types of glomerular lesions have since been described in association with hepatitis B virus (HBV) carriage; however, the most striking is still MN.

Hepatitis B virus (HBV) virology
HBV is a hepatotropic, double-stranded DNA virus, belonging to the family Hepadnaviridae. HBV has a double-shelled virion 42–47 nm in diameter, a 27-nm internal core, an excess of incomplete 22-nm spheres and a circular DNA, with a length varying between 3000 and 3300 base pairs. The DNA genome contains only four genes that encode viral proteins. These include the surface (S) gene, which encodes the three forms of HBsAg, the pre-core/core (PC/C) gene, which encodes the core protein and hepatitis B e antigen (HBeAg), the X gene, which encodes the X protein, and the polymerase (P) gene, which encodes the viral DNA polymerase. HBV is itself not cytopathic; hepatitis develops as a result of the host’s immune reaction toward infected hepatocytes. HBV utilizes a replication strategy closely related to retroviruses, in that transcription of RNA into DNA is a critical step. Unlike retroviruses, HBV DNA is not integrated into host cell DNA during replication. After a HBV particle binds to and enters a hepatocyte, HBV DNA enters the cell nucleus and is converted into covalently closed circular DNA (cccDNA), which is highly stable acting as the intermediate template for transcription of RNA copies. This pre-genomic mRNA is transported to the cytoplasm and has the dual functions of acting as a template for synthesis of new HBV DNA, and carrying genetic information to direct the synthesis of viral proteins.

Epidemiology
Today, an estimated 350–400 million people worldwide are infected with HBV. The reported prevalence of HBV-associated nephropathy, particularly MN, closely parallels
HEPATITIS B-ASSOCIATED RENAL DISEASES

the geographic patterns of prevalence of HBV. HBV infection occurs throughout the
world and is endemic in developing countries, such as Africa, Eastern Europe, the
Middle East, Central Asia, China, Southeast Asia, the Pacific Islands and the Amazon
basin of South America (prevalence rates up to 10% or higher).

In endemic areas, transmission is usually vertical from infected mother to child. Horizontal transmission occurs via direct contact with blood (as in blood transfu-
sions) or mucous membranes (as in sexual contacts), or via the percutaneous route on
contact with blood or body fluids (as in illicit intravenous drug use and needle-sharing
practices).

Definition of HBV-associated glomerulonephritis (GN)
The pathogenetic role of HBV in renal disease has attracted much attention, since
Combes et al. in 1971 reported GN with immune complexes of HBsAg and its
antibody (anti-HBs) in a patient infected with HBV. Previous observations of a
greater-than-expected incidence of chronic HBsAg carriers among the patients with
various forms of glomerulonephritides compared with the general hospital population
in different geographic areas, tend to support the hypothesis of a pathogenetic association
between chronic HBV infection and GN. Various morphological patterns including
MN, mesangiocapillary GN, minimal change nephropathy and mesangial proliferative
GN have since been described.

The only definitive means to prove that a particular GN is aetiologically associated
with chronic HBV infection is to fulfil the following criteria:
1) the pathology should be reproducible in experimental animals infected with the
virus
2) demonstration of HBV-specific antigen(s) in the glomerulus
3) disappearance of the pathological lesion with eradication of the virus.

Unfortunately, solid research work reproducing the GN in infected experimental animals
was lacking until recently. Inoculating primates with varying amounts of human
plasma containing HBsAg resulted in lesions consisted of progressive focal GN with
mesangial alterations that developed over a period of 4–10 months after inoculation.
The most likely explanation is immune complex deposition. The possibility that the
immune complex deposition may have resulted from an antibody response to human
plasma that was injected can be excluded, as in rabbits injected with a single dose of
bovine serum albumin any renal lesions were reversible and undetectable by the fourth
week after injection. In primates, the renal lesions were progressive and a temporal
progression of these lesions was observed that was similar to that reported in the
chronic bovine serum albumin-rabbit model.

Recent observations from chronic woodchuck hepatitis virus infection in woodchucks
revealed three types of GN, namely, MN with capillary HBcAg deposits, mesangial
proliferative GN with mesangial deposits of HBsAg, and mixed membranous
and mesangial proliferative GN with capillary deposits of HBcAg and mesangial
deposits of HBsAg. The animal model of woodchuck hepatitis may be valuable for
experimental study of the natural progression of renal lesion, as its pathological findings are similar to those of humans. MN is the most common type of GN in humans and is particularly frequent in male children.\(^3\) Mesangial proliferative forms with IgA deposits appear to be more common in adults.\(^2\) Woodchucks with a membranous component appeared to be younger, whereas woodchucks with mesangial proliferative GN appeared to be older. The male/female ratio of the affected animals was significantly greater than that of the chronic carrier population. Thus, the pattern of occurrence of these types of GN was similar to that observed in human kidneys with the exception of HBeAg, as the woodchuck hepatitis antigen system has not been characterized.

Complete disappearance of the pathology with eradication of the virus in human beings is not easily demonstrated because of the ethical consideration of renal biopsy in patients in clinical remission. Hence, the diagnosis of HBV-associated GN, at present, depends on the demonstration of HBV-specific antigen(s) in the glomeruli.

**Pathology of HBV-related GN**

**Membranous nephropathy**

This pathological entity remains the best recognized glomerulopathy associated with chronic HBV infection.

**Mesangial proliferative GN**

Co-existence of mesangial proliferative GN with predominant mesangial IgA deposits and persistent hepatitis B surface antigenaemia was first reported in five patients by Nagy et al.,\(^5\) and later in two patients by Sluzarczuk et al.\(^6\) Mesangial IgA nephropathy associated with chronic HBV infection is subsequently supported by other investigators.\(^7\)

**Mesangiocapillary nephropathy**

This is also a well-recognized glomerulopathy associated with chronic HBV infection.

**Focal glomerulosclerosis**

The association between chronic HBV infection and focal glomerulosclerosis remains unclear. Focal glomerulosclerosis in HBsAg carriers is likely to be secondary to progression of other types of HBV-associated GN or a sequel of hepatic cirrhosis.

**Minimal change nephropathy**

Although minimal change nephropathy has been reported in chronic HBV carriers, the pathogenetic association is unlikely as glomerular deposition of immunoglobulin and HBV antigen is rarely observed. Furthermore, the prevalence of hepatitis B surface antigenaemia in nephrotic patients with minimal change nephropathy is not higher than that of the general population.\(^2\)
Polyarteritis nodosa/microscopic polyangiitis

The association between polyarteritis nodosa (PAN) and hepatitis B was first reported in 1970. Subsequently, the presence of HBsAg in the serum among various series has been noted in 0 to 54% of cases of PAN (reviewed by Johnson and Couser3). Of interest is the observation that PAN associated with hepatitis B has been primarily reported in Europe and the USA, where the prevalence of the HBsAg carrier state is greatest in adults, and infection is usually acquired via a parenteral route. In contrast, PAN associated with hepatitis B is uncommon in endemic areas such as Southeast Asia and Africa where most infection occurs in childhood via transmission from parents or siblings. Furthermore, the variability in incidence of HBsAg in PAN within the USA may be partially explained by the underlying prevalence of intravenous drug abuse and the HBV carrier rate at the various reporting centres. Thus, in New York, up to 40% of PAN is HBV-associated as opposed to Ann Arbor, Michigan and Rochester, Minnesota, where the rates are from 6% to 25%. A review of PAN and microscopic polyangiitis (MPA) failed to demonstrate any association between HBV and systemic vasculitides.8 Retrospective analysis of 115 patients with HBV-associated PAN revealed when renal involvement is present; the pathology is vasculitic with no case of glomerulonephritis.9 Despite the earlier observation, the aetiological association between chronic HBV infection and PAN/MPA has not been substantiated.

Nature of HBV antigens in glomeruli

HBV-associated GN is generally considered to be an immune complex-mediated disease. Three distinct antigens, HBsAg, HbcAg and HBeAg, have been detected by immunofluorescent studies in renal biopsies from patients with HBV-associated GN. Both HbcAg and HBsAg have a molecular weight in excess of 200000 Da. HBeAg, which is a part of the viral nucleoprotein derived from denatured HbcAg, is found in two forms with molecular weights of 19000 and 300000 Da. HBeAg is expected to be capable of inducing MN by being preferentially deposited along capillary wall.10 If HBV antigens with a lower molecular weight (i.e. HBeAg) induce MN, one would predict mesangial proliferative or mesangiocapillary GN associated with chronic HBV infection would show immune complexes with high molecular weight antigens (i.e. HBsAg). Furthermore, a mixed picture of mesangial IgA and MN should be seen in HBV-associated GN as immune complexes with different molecular weights may be present simultaneously in some of these patients. Such a glomerulopathic entity has been reported with mesangial HBsAg and capillary HBeAg deposits,11,12 thus confirming the above-mentioned hypothesis and also complying with the experimental findings of Germuth et al.13

HBV-associated MN

Glomerular capillary depositions of HBsAg, HbcAg and HBeAg in HBV-associated MN have been observed by various investigators using different reagents. Hirose et al.12 had used F(ab′)2 fragments of anti-HBsAg monoclonal antibody to demonstrate that capillary deposits were HBeAg in nature. Using the same F(ab′)2 fragment of anti-HBeAg monoclonal antibody and another monoclonal antibody against
HBeAg, Lai et al.\textsuperscript{14} demonstrated capillary HBeAg deposits in two-thirds of the biopsies, and the incidence was similar to that reported by Hirose et al.\textsuperscript{12} However, identical capillary HBeAg immunostaining was demonstrated when polyclonal antibody was used.\textsuperscript{14} Further studies revealed that commercial polyclonal anti-HBeAg antiserum contains both anti-HBeAg and anti-HBcAg activities.\textsuperscript{14} This can be explained by the fact that the HBeAg is an integral component of HBcAg.

**HBV-associated mesangial proliferative GN with mesangial IgA deposits**

Lai et al.\textsuperscript{2} had reported the detection of glomerular HBsAg in 30\% of renal biopsies from patients with co-existing IgA nephropathy and persistent hepatitis B surface antigenemia by polyclonal antisera. Contrary to the findings in MN, glomerular HBeAg deposits were not detected in the renal biopsy from IgA nephritic patients with co-existing chronic HBV carriers using both polyclonal and monoclonal antibodies. Mesangial deposits of HBsAg similar to the distribution of IgA immunostaining were detected in 40\% and 21\% of the renal biopsies by polyclonal and monoclonal antibodies respectively,\textsuperscript{14} suggesting HBsAg rather than HBeAg may play a pathogenetic role in some of the patients with IgA nephropathy associated with chronic HBV infection.

**HBV-associated mesangiocapillary GN**

Well-documented reports of such glomerulopathic entities both demonstrated simultaneous glomerular deposition of HBeAg and HBsAg,\textsuperscript{15} supporting the hypothesis that immune complexes with HBV antigens of different molecular weights could induce a mixed pattern of GN as shown previously in cases of mixed IgA and MN.\textsuperscript{11}

**Immunopathology of HBV-associated GN**

Animal experiments and observations on human subjects have demonstrated that HBV-containing immune complexes may be formed in the course of HBV-induced acute and chronic hepatitis. Immune complex-mediated GN requires a continuous supply of antigen and a sustained antibody response and, apparently, these requirements seem to be met in chronic HBV carriers. Despite the detection of circulating immune complexes in HBV-associated MN, HBV antigen(s) forming an integral part of the circulating immune complexes in these patients has not been unequivocally demonstrated. This raises the question of immune complex formation \textit{in situ} (which occurs in primary MN) in HBV-associated MN.

Extrahepatic HBV replication occurs in human subjects but it is unclear whether viral replication occurs within the kidney in these patients with HBV-associated GN. Spherical virus-like particles of 40–50 nm diameter have been demonstrated within the glomerular electron-dense deposits in renal biopsies from patients with HBV-associated GN. HBV viral replication in the kidneys of some of these HBV-associated GN is suggested by the localization of HBV DNA genome by in situ hybridization in glomeruli.\textsuperscript{16,17} This mechanism is supported by the findings in woodchucks. De novo synthesis of viral antigens in viral infection has been demonstrated in renal tissues of woodchucks and small amounts of viral-specific mRNA, including full-length transcripts,
have been demonstrated in the glomeruli of woodchuck hepatitis virus-infected woodchucks.\textsuperscript{18} Lin\textsuperscript{19} had detected HBV DNA in glomeruli and tubular epithelia by in situ hybridization in patients with early-onset HBV-MGN but the glomerular HBV DNA was exclusively extracellularly located. It is plausible that such presence of HBcAg or HBV DNA results from endocytosis by proximal tubular epithelia when the HBV DNA in the urinary filtrate crosses their luminal borders. Alternatively, the presence of HBV DNA in the tubular epithelia could indicate HBV replication in the tubular epithelia and these findings are in keeping with other transgenic mice studies revealing the expression of viral genome of HBcAg or HBeAg only in convoluted tubular epithelia. Using polymerase chain reaction and in situ hybridization, Lai et al.\textsuperscript{20} demonstrated frequent presence of HBV DNA within the cytoplasm of the renal proximal tubules in different HBV-associated glomerulonephritides of long duration. However, they detected HBV transcriptionally active genomes or mRNA in the glomeruli of these biopsies by in situ hybridization with a HBV-specific RNA probe. The HBcAg mRNA was localized mainly in epithelial cells in HBV-associated MN and in both epithelial and mesangial cells in HBV-associated IgA nephropathy. These findings strongly suggest the notion that nephropathy may arise from immune complex formation in situ.

**Clinical findings**

**Symptoms and signs**

Paediatric and adult patients tend to have slightly different clinical manifestations of HBV-related MN (Table 23.1). In children, there is a strong male preponderance, and the most frequent presentation is nephrotic syndrome together with microscopic haematuria, and normal or mildly impaired renal function. Paediatric chronic HBV carriers often do not have overt liver disease, and transaminase levels are usually normal. In adults, proteinuria or the nephrotic syndrome are the most common manifestations, although male predominance is less obvious than that observed in children. In addition, adults are more likely than children to have hypertension, renal dysfunction and clinical evidence of liver disease.

The prognosis of HBV-associated MN in children is favourable with stable renal function and high rates of spontaneous remission reported in several high prevalence areas, including Hong Kong, South Africa and Turkey.\textsuperscript{21} On the other hand, adults with HBV-associated MN typically develop progressive disease. In Hong Kong, up to 29\% of patients had progressive renal failure, and another 10\% developed ESRD over 5 years.\textsuperscript{22} The prognosis is even worse in patients with nephrotic-range proteinuria and overt hepatitis at presentation, with over 50\% of patients requiring renal replacement therapy over 3 years.\textsuperscript{23} Prognosis is worse in those with vertical versus those with horizontal transmission and also worse in endemic versus sporadic infection.

**Laboratory and pathological findings**

Laboratory tests to be followed for diagnostic purposes and also to assess response to treatment include standard liver biochemistries (serum alanine aminotransferase, $\gamma$-glutamyltransferase, and bilirubin levels) and HBV serologies (HBsAg, HBeAg, anti-HBe,
and anti-HBc antibodies). HBeAg is present in 80% of patients, who may also have high titres of anti-HBc. Subjects with biochemical hepatitis should also be tested for circulating HBV DNA levels, and undergo liver biopsy. In addition, α-fetoprotein assay could be an important adjunct. Serum C3 and C4 levels may be low in 20–50% of patients.

Light microscopic findings are similar to that of idiopathic MN, with some differentiating features. The characteristic glomerular lesion is diffuse thickening of glomerular capillary walls to form thick ‘membranes’. It is now firmly established that this alteration is caused by immune complexes that accumulate subepithelially on the outer aspect of the GBM that assumes the ‘membranous’ morphology in a stepwise manner. Other pertinent light microscopic findings are reflected by the reactive structural changes of the GBM induced by immune complexes. Therefore special stains highlighting the GBM like methenamine silver and periodic acid-Schiff (PASM or silver stain) or trichrome stain are more useful. The earliest change on silver staining is a mottled appearance best seen on tangential sections and represents slight indentations of the GBM by immune complexes adhering to its surface. The most specific change of the GBM is the so-called spike formation. These are projections of GBM material between immune complexes that lead to a saw tooth-like appearance of the GBM. This pattern is pathognomonic of full-blown MN. Disease progression results in a diffuse thickening of the GBM. The major constituents of the immune complexes are IgG together with C3. IgM, IgA and C1q may be present. Ultrastructural findings typically consist of both subepithelial and occasional subendothelial deposits. The presence of subendothelial deposits, sometimes referred to as mesangiocapillary GN type III changes, favours a case of MN to be secondary such as HBV-associated rather

| Table 23.1 Clinical presentation of hepatitis B virus (HBV)-associated membranous nephropathy |
|-----------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Route of HBV infection:           | Children                        | Adult                          |                                |                                |
| Vertical or horizontal within family members | +                               | + (in endemic areas)           |                                |                                |
| Intravenous drug abuse            | –                               | + (in non-endemic areas)       |                                |                                |
| Blood transfusion                 | –                               | + (in non-endemic areas)       |                                |                                |
| Homosexually                      | –                               | + (in non-endemic areas)       |                                |                                |
| Male:female ratio                 | 4:1                             | 2–3:1                          |                                |                                |
| History of liver disease          | Absent                          | Absent in endemic areas        |                                |                                |
| Abnormal liver functions          | Uncommon                        | Mild rise in ALT               |                                |                                |
| Presenting symptoms               | Nephrotic syndrome              | Nephrotic syndrome/proteinuria |                                |                                |
| Hypertension                      | <25%                            | 25–40%                         |                                |                                |
| Renal insufficiency               | Rare                            | Occasional                     |                                |                                |
| Serum positivity for HBeAg and anti-HBc | + (88.2%)                     | + (87.5%)                      |                                |                                |
than idiopathic. The presence of mesangial proliferation on light microscopy is helpful in distinguishing this form of secondary from idiopathic MN.

The light microscopic finding of HBV-associated mesangial proliferative GN with mesangial IgA deposits resembles that of primary IgA nephropathy. Regardless of the pathological finding, it is important to localize HBV-specific antigens in the biopsy. To document an aetiological association between HBV and MN or other forms of glomerular lesion, demonstration of HBV-specific antigens by immunofluorescence is indispensable. Furthermore, HBV DNA and mRNA have been detected in the glomerulus and tubular epithelia by polymerase chain reaction and in situ hybridization with specific HBV RNA probes.20

**Treatment**

Unlike childhood disease in which there is a high rate of spontaneous remission,24 adults with HBV-associated MN typically develop progressive disease.22 Various strategies have been tried, although an ideal agent has yet to be found. Treatment for HBV-associated renal disease should ideally achieve the following objectives:

1) amelioration of nephrotic syndrome and its complications, such as hyperlipidaemia, oedema, infection and venous thrombosis
2) preservation of renal function
3) normalization of liver function and prevention of hepatic complications of HBV
4) permanent eradication of HBV.

In view of the immune complex nature of the disease, immunosuppressive therapy, similar to that applied in the idiopathic form of the disease, was once fashionable. Although corticosteroid has been previously reported to achieve symptomatic relief in isolated cases, the contemporary view is that steroids and cytotoxic agents may cause deleterious hepatic flares or even fatal decompensation by enhancing viral replication on treatment withdrawal.25

Another approach is treatment with an anti-viral agent. Interferon-α is a naturally occurring cytokine produced by B lymphocytes, null lymphocytes and macrophages, and possesses anti-viral, anti-proliferative and immunomodulatory effects. Although reported to be useful in children, interferon-α has produced mixed results in adults with HBV-associated MN.

The introduction of the nucleoside analogue, lamivudine, has revolutionized the treatment of chronic HBV infection. A potential limitation of prolonged treatment with lamivudine is the emergence of drug-resistant strains due to the induction and selection of HBV variants with mutations at the YMDD motif of DNA polymerase. Another agent that might be considered in cases of lamivudine resistance is adefovir dipivoxil, an acyclic nucleotide analogue, which is effective against both lamivudine-resistant HBV mutants as well as wild-type HBV. However, this agent is potentially nephrotoxic and there is no clinical trial on its efficacy in HBV-related MN that does not respond to lamivudine treatment. There are data to suggest that the recommended dose of 10 mg adefovir dipivoxil is associated with a lower risk of nephrotoxicity.26
Unlike chronic liver disease due to hepatitis B in which well-designed placebo-controlled clinical trials are available, studies on the treatment of HBV-associated GN are usually case reports or small-sample uncontrolled trials. In order to draw reliable conclusion, such clinical trials should fulfill a set of criteria including the results of primary anti-viral therapy, the virological response (VR) and clinical (CR) response as a clinical end-point. Table 23.2 summarizes five controlled clinical trials (CCTs), case-control or cohort studies that provide data on interferon as an anti-viral treatment for HBV-related GN.\textsuperscript{22,27–30} The overall estimate for sustained remission of proteinuria induced by interferon therapy was 50%. This response is higher than that typically reported in patients with chronic hepatitis B and normal renal function. In the general population, interferon therapy has a beneficial effect in 30–40% of patients with chronic hepatitis B who respond by clearing HBeAg from serum.\textsuperscript{31} It appears the response rate is higher in children and adult patients from non-endemic areas. The natural history of HBV-associated nephrotic syndrome in children tends to show gradual improvement in many cases. For patients from non-endemic areas, the shorter duration of infection may favor a better VR to anti-viral therapy. However, patients from endemic areas who acquire HBV infection early in neonate or at very young age and those with chronic renal insufficiency at diagnosis tend to have less favourable response to interferon therapy.

Table 23.3 summarizes nine reports (one controlled clinical trial and eight case reports) on the therapeutic effect of lamivudine in HBV-associated GN.\textsuperscript{33–40} The overall clinical and virological responses with lamivudine were better than that of interferon. The link between a sustained proteinuria remission and HBeAg clearance was stronger with lamivudine-based studies than interferon-based studies.

The efficacy and safety of adefovir dipivoxil were examined in six patients with HBV-associated GN.\textsuperscript{41} After 1-year treatment (100 mg daily), the disease subsided fully in three patients (50%) and partially in two. The negative conversion rates of HBV DNA and HBeAg at 6 months were 83.3% and 66.7% respectively. These findings suggest a therapeutic value of adefovir dipivoxil in HBV-associated GN but an optimal dosage must first be established to prevent nephrotoxicity.\textsuperscript{26}

**Prevention**

Short of an ideal agent for treatment of HBV-associated glomerulopathy, active immunization remains the most effective measure of immunoprophylaxis. Prevention by an effective vaccination programme is far superior to anti-viral treatment despite the promise shown by new anti-viral therapy. These medications are expensive and the treatment period is prolonged with no consensus opinion of treatment duration. Vaccination for all newborns in some endemic areas has dramatically reduced the incidence of chronic HBV infection and its associated complications in children and adolescents. In Taiwan, the introduction of active immunization to all newborns since 1984 has led to a dramatic (10-fold) decline in the incidence of neonatal HBV infection and its subsequent sequelae.\textsuperscript{42} A study from Shanghai in China revealed that only 3.5% of vaccinated children developed HBV-related GN compared with 12.6% in non-vaccinated children.\textsuperscript{43} Furthermore, the incidence of HBV-related GN fell by
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Country</th>
<th>Patient number</th>
<th>Mean age (years)</th>
<th>MN (%)</th>
<th>HBeAg (%)</th>
<th>Creatinine clearance (ml/min)</th>
<th>Proteinuria (g/day)</th>
<th>IFN dose*, MU</th>
<th>IFN duration (months)</th>
<th>Follow-up (months)</th>
<th>HBsAg clearance (%)</th>
<th>HBeAg clearance (%)</th>
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<td>5</td>
<td>27</td>
<td>100</td>
<td>100</td>
<td>87 (36–130)</td>
<td>3.5+1.5</td>
<td>3 x 3/wk</td>
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<td>12</td>
<td>0</td>
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<td>CCT</td>
<td>Taiwan</td>
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<td>6</td>
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<td>116±8</td>
<td>4.1+0.8</td>
<td>5 x 3/wk</td>
<td>12</td>
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<td>60</td>
<td>80</td>
<td>100</td>
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<td>82 (29–127)</td>
<td>7 (1–11.5)</td>
<td>5 x 7/wk</td>
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<td>25</td>
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<td>105 (76–141)</td>
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<td>4</td>
<td>6</td>
<td>0</td>
<td>58</td>
<td>42</td>
</tr>
</tbody>
</table>

*Recombinant interferonα-2b.

CCT, clinical controlled study; Co, cohort study; MU, million units; NA, not available; P, prospective; R, retrospective.
Table 23.3 Characteristics and outcome of published studies on HBV-associated GN treated with lamivudine

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Country</th>
<th>Patient number</th>
<th>Age or mean age (years)</th>
<th>MN</th>
<th>HBeAg</th>
<th>Serum creatinine (mg/dl)</th>
<th>Proteinuria (g/day)</th>
<th>LAM, mg/day</th>
<th>LAM duration (months)</th>
<th>Follow-up (months)</th>
<th>HBsAg clearance</th>
<th>HBeAg clearance</th>
<th>Proteinuria (sustained remission)</th>
</tr>
</thead>
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<tr>
<td>Connor</td>
<td>CR</td>
<td>Australia</td>
<td>1</td>
<td>6</td>
<td>Yes</td>
<td>Positive</td>
<td>Normal</td>
<td>&gt;300†</td>
<td>100</td>
<td>12</td>
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<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
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<td>CR</td>
<td>Canada (Vietnamese)</td>
<td>1</td>
<td>5</td>
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<td>NA</td>
<td>&gt;3</td>
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<td>NA</td>
<td>Relapse after stopping LAM</td>
</tr>
<tr>
<td>Tang</td>
<td>CCT</td>
<td>Hong Kong</td>
<td>10</td>
<td>48±13</td>
<td>100%</td>
<td>70%</td>
<td>0.98±0.18</td>
<td>4.9±2.4</td>
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<td>12</td>
<td>49</td>
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<td>50%</td>
<td>70%</td>
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<tr>
<td>Gan</td>
<td>CR</td>
<td>Canada (Chinese)</td>
<td>2</td>
<td>44 and 46</td>
<td>Yes</td>
<td>Positive</td>
<td>NA</td>
<td>7.1 and 8.1</td>
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<td>12</td>
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<td>Japan</td>
<td>1</td>
<td>37</td>
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<td>Positive</td>
<td>GFR 25 ml/min</td>
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<td>100</td>
<td>48</td>
<td>108</td>
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<td>Normal</td>
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<td>39</td>
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<td>4.5</td>
<td>100</td>
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<td>9</td>
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<td>CR</td>
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<td>22</td>
<td>Yes</td>
<td>Positive</td>
<td>0.9</td>
<td>6.0</td>
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<td>6</td>
<td>13</td>
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<tr>
<td>Mesquita</td>
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<td>Belgium</td>
<td>1</td>
<td>28</td>
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<td>Negative</td>
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<td>14.5</td>
<td>100</td>
<td>84</td>
<td>84</td>
<td>NA</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

*Pre-core HBV mutant.
†Urine albumin-to-creatinine ratio (normal 0–3 mg/mmol).
CCT, clinical controlled study; CR, case report; LAM, lamivudine; MPGN, membranoproliferative glomerulonephritis; NA, not available.
50% within 10 years after the introduction of a vaccination programme in an endemic region. Similar fall of incidence rate of HBV-related MN was reported in the paediatric population in South Africa.\textsuperscript{44} In 2003, the World Health Organization recommended that all countries provide universal HBV immunization programmes for infants and adolescents.\textsuperscript{45}

**Take home points**

1. HBV-related glomerulopathy is associated with chronic immune complex formation \textit{in situ}.
2. The pathologies include MN, mesangiocapillary nephropathy and mesangial proliferative GN with IgA deposits.
3. The development of individual pathology is related to the size of the HBV antigens.
4. The glomerulopathy progresses slowly with development of end-stage renal failure if untreated.
5. Anti-viral agents are effective in slowing the progression of the renal failure. Symptomatic improvement occurs with eradication of the virus.
6. Prevention by an effective vaccination programme is far superior to anti-viral treatment despite the fact that new anti-viral therapy is promising on a long-term carrier.
7. A national vaccination for newborn in endemic areas is strongly recommended.

**Acknowledgments**

Part of the work was supported by the L & T Charitable Foundation and the House of INDOCAFE.

**References**

\* of special interest.
\*\* of outstanding interest.

REFERENCES


   * Demonstration of IgA nephropathy as a form of HBV-related glomerulopathy in endemic areas.


   ** Demonstration of the influence of the antigen size in the development of individual pathology entity.


   * Evaluation of the antibodies used in studying HBV antigens and their cross-reactivities.


   ** A definitive confirmation of chronic immune-complex formation in situ as the pathogenetic mechanism in HBV-related glomerulopathy.


** This article describes the natural course of HBV-related membranous nephropathy and a systemic study of specific anti-viral agent.


** A report of the controlled trial in using lamivudine in HBV-related membranous nephropathy.


* A report of the use of interferon \(\alpha\) recent-onset in HBV-related glomerulopathy in non-endemic area


REFERENCES


* Demonstration of the effectiveness of HBV vaccination in reducing HBV-related glomerulopathy.


Introduction

The mortality and morbidity of human immunodeficiency virus (HIV)-infected persons has improved dramatically in the era of anti-retroviral therapy (ART). Although the overall incidence of rheumatic complications has declined, HIV-infected individuals remain at an increased risk to develop musculoskeletal pathology with even new complications emerging.1–3

Laboratory abnormalities

Autoimmune phenomena are frequent in HIV-infected patients. They result from either polyclonal B cell stimulation or T cell expansion after the initiation of ART and do not necessarily reflect autoimmune disease.4 Laboratory findings in sera of HIV-infected persons may consist of a positive rheumatoid factor or anti-nuclear antibodies.5–7 Anti-phospholipid antibodies were found in up to 94% of HIV-infected persons and anti-β2 glycoprotein-1 antibodies in up to 47%, whereas the lupus anticoagulant was mostly negative. The relatively low prevalence of anti-glycoprotein-1 antibodies and the observation that anti-cardiolipin autoantibodies are often transient and disappear with ART may explain the fact that the full picture of the anti-phospholipid syndrome is uncommon.8

Articular complications

Arthralgia

In prospective studies, about 45% of HIV-infected persons complain of joint pain.7 Arthralgia is most frequently observed in the knees, shoulders and elbows.7 The literature describes an intermittent articular syndrome of unknown aetiology, which lasts only a few hours; its high pain intensity may require opioid analgesics.9,10

In the setting of acute HIV infection, joint pain is a typical symptom of the flu-like illness observed after the incubation period of a few days to weeks. Other symptoms of acute HIV infection consist of fever (80–88%), rash (51–58%), oral ulcers (8–37%), myalgia (49–60%), pharyngitis (43%) and malaise (68–73%).11 The diagnosis hinges on the presence of HIV-1 RNA in the absence of HIV-1 antibodies.
HIV-associated arthritis

HIV-associated arthritis can manifest at any time during the chronic course of HIV-infection; its prevalence was 1% in a tertiary care setting. HIV-associated arthritis is usually a non-erosive oligoarthritis of the lower extremities, which after less than 6 weeks is self-limited. The lack of enthesopathy, mucocutaneous involvement and HLA-B27 gene expression differentiates HIV-associated arthritis from Reiter’s syndrome. HIV was isolated from the synovial fluid in only one report.

Reiter’s syndrome

Reiter’s syndrome was diagnosed in 0.4–10% of HIV-infected subjects and presents as an asymmetric oligoarthritis, with enthesopathy, sacroileitis or extra-articular manifestations such as conjunctivitis, circinate balanitis, urethritis, and keratoderma blennorrhagicum. Therapy consists of sulfasalazine and effective ART. Tumour necrosis factor (TNF)-α inhibitors were also used successfully.

Psoriatic arthritis

The incidence of psoriatic arthritis is increased in HIV-infected patients compared with the general population, and its severity parallels the impairment of the immune system. Immune reconstitution with ART or anti-TNF-α biologics have successfully improved psoriatic skin and joint manifestations.

Septic arthritis

Immunodeficiency is a risk factor for infections in joints, tendon sheaths and bursae, although there is no clear association with CD4+ counts. Joint infections are observed in about 1% of HIV-infected persons. Some studies, however, question whether HIV infection actually predisposes for septic arthritis and suggest that intravenous drug abuse actually represents a more important risk factor.

Septic arthritis usually affects the large joints of the legs in young men. Sterno-clavicular joints are a frequent target in intravenous drug users. Pyogenic organisms predominate at CD4+ counts above 250/µl, opportunistic pathogens are observed at CD4+ counts below 100/µl. Opportunistic infections may become symptomatic only when the immune system is reconstituted after ART has been commenced.

Gout

Hyperuricaemia has been observed in up to 42% of HIV-infected individuals. The annual incidence of gout is an order of magnitude higher than in the normal population. Serum urate may be elevated as a consequence of increased cell turnover or of ART (particularly with didanosine and stavudine). Urate elevation may result from the mitochondrial toxicity of these anti-retrovirals, which stimulates lactate production and urate reabsorption in the renal tubules.

Myopathy

The most important muscular complications in HIV patients consist of rhabdomyolysis, zidovudine myopathy, polymyositis, wasting syndrome and pyomyositis.
Rhabdomyolysis may either complicate primary HIV infection or ART due to either a pharmacological interaction between protease inhibitors and statins at hepatic cytochrome P, or hypersensitivity to abacavir, a nucleosidic reverse transcriptase inhibitor. Among the statins, lovastatin and simvastatin should be avoided, whereas pravastatin is the agent of choice with simultaneous protease inhibitor therapy. The formation of macroenzyme CK must be considered when the creatine kinase (CK) MB isoenzyme activity is disproportionately elevated. Macro CK is observed in approximately half of HIV patients treated with tenofovir, another reverse transcriptase inhibitor.

A myopathy is induced by zidovudine, an anti-retroviral agent that blocks the replication of mitochondrial DNA. Zidovudine myopathy represents perhaps the most frequent muscle complication in HIV patients. Patients complain of dynamic or static muscle weakness, although the serum CK is usually not, or only minimally, elevated. Muscle histology shows a high prevalence of ragged-red fibres and cytochrome c-oxidase negative fibres. Zidovudine myopathy resolves after the discontinuation of the causative agent.

HIV-associated polymyositis may be observed at any stage of HIV infection. The muscle is typically infiltrated by CD8+ T lymphocytes. Half of the patients also have involvement of other tissues in terms of a diffuse infiltrative lymphocytosis syndrome (DILS). HIV-associated polymyositis responds to immunosuppressive therapy or resolves spontaneously.

The acquired immunodeficiency syndrome (AIDS)-defining wasting syndrome has now become rare where ART is available. Muscle biopsy usually reveals unspecific type II fibre atrophy or mild neurogenic atrophy without inflammation.

Pyomyositis mainly affects men with low CD4+ counts. Staphylococcus aureus is the pathogen most frequently isolated.

Bone complications

Osteonecrosis

HIV-infected patients have about a 100-fold increased risk of osteonecrosis compared with the general population. Osteonecrosis is most frequently localized at the hip and occasionally bilateral. Eleven per cent of initially asymptomatic patients eventually require hip replacement. Chronic inflammation, anti-cardiolipin autoantibodies and ART with a protease inhibitor may be predisposing factors.

Bone mineral loss

Low bone mineral density is highly prevalent in HIV-infected patients and is of multifactorial origin. HIV-infected persons are subject to an increased risk of osteoporotic fractures compared with population-based controls, even with normal bone mineral density. Chronic infection and protease inhibitor treatment were implicated as risk factors but later refuted in longitudinal studies. It is not known if bisphosphonates that increase bone mass also prevent fractures in HIV-associated osteopenia.

Osteomalacia

The anti-retroviral nucleotide analogue tenofovir may induce Fanconi’s syndrome and symptomatic osteomalacia due to tubular phosphate loss. Skeletal scintigraphy may
reveal pseudofractures (Looser’s zones), which are not evident in routine radiographs.46 Osteomalacia symptoms improve when tenofovir is discontinued.46

Osteomyelitis

Bone infections tend to occur at lower CD4+ counts than joint infections. *Staphylococcus aureus* is the most frequent pathogen but polymicrobial infections are also observed.20

Multi-system manifestations

Vasculitis

A wide range of vasculitic manifestations were reported in HIV-infected individuals. Cryoglobulins (types II and III) are most frequently found with simultaneous hepatitis C virus infection.47,48 Cryoglobulinaemia may present at the skin as leucocytoclastic vasculitis, with mononeuritis multiplex, arthritis or glomerulonephritis.47,48 In the setting of hepatitis C virus co-infection, cryoglobulinaemic symptoms mostly subside with hepatitis C treatment.38,49

Vasculitic complications of larger arteries in HIV-infected patients include coronary arteritis and aneurysms in African patients.49 Infectious causes should be ruled out. Among HIV-infected patients with stroke, vasculitis was identified in 13%. Cerebral vasculitis can manifest immediately after HIV seroconversion or in more advanced disease. Granulomatous angitis of the central nervous system is not specific to HIV and is seen in many conditions of immune dysfunction.50 Central nervous system vasculitis may also be triggered by opportunistic infections such as varicella zoster or cytomegalovirus. Polyarteritis nodosa and a Behçet’s-like disease were observed in association with HIV.

DILS

DILS is characterized by CD8+ lymphocytosis in the peripheral blood and CD8+ T cell infiltration in organs as an excessive immune response to HIV. DILS is observed in up to 3% of HIV-infected patients51 and resembles Sjögren’s syndrome by its bilateral painless parotid gland enlargement, lacrimal gland enlargement and sicca symptoms.51 DILS mostly manifests years after HIV-seroconversion. Extraglandular complications consist of lymphoid interstitial pneumonitis (31%), muscular (26%) and hepatic (23%) involvement. A disproportionately greater degree of salivary gland enlargement and extraglandular disease, a low frequency of autoantibodies and rheumatoid factor, and the association to HLA DR5 and DRB1 distinguish DILS from Sjögren’s syndrome. DILS improves with ART.

Sarcoidosis

CD4+ lymphocytes play an important role in granuloma formation. Thus, most patients with symptomatic sarcoidosis in the context of HIV infection have peripheral CD4+ lymphocyte counts above 200 cells/μl or marked CD4+ lymphocyte increases following the initiation of ART.3,52,53 Granulomatous infections with Pneumocystis jiroveci, Cryptococcus, Toxoplasma, cytomegalovirus and mycobacteria must be ruled out. Most patients with sarcoidosis improve with immunosuppression and simultaneous ART.
Systemic lupus erythematosus (SLE)
Pre-existing SLE generally improves during the natural course of HIV infection due to the importance of CD4+ T cells in the pathogenesis of SLE. Conversely, SLE can flare with immune recovery under ART.\(^3\),\(^5\) SLE and HIV infection may be difficult to distinguish because oral ulcerations, sicca symptoms, alopecia, arthritis, fever and neuropathy can be features of both conditions. In the laboratory both SLE and HIV infection can feature cytopenia, hypergammaglobulinaemia, anti-nuclear and anti-phospholipid antibodies. Anti-dsDNA antibodies are perhaps more specific for SLE.\(^5\),\(^5\) Anti-HIV antibody tests can be falsely positive in SLE even in Western blot analyses and must be confirmed in antigen- or nucleic acid-based assays.

Anti-rheumatics in HIV-infected individuals
For symptomatic relief of musculoskeletal symptoms, non-steroidal anti-inflammatory drugs can be used in HIV-infected individuals. Indomethacin may be preferred because clinically relevant doses were shown to inhibit HIV replication \textit{in vitro}.\(^5\) Sulfasalazine and hydroxychloroquine have been successfully used in Reiter’s syndrome and HIV-associated arthropathy.\(^5\),\(^5\) In a dose of 800 mg/d hydroxychloroquine had anti-viral activity equal to zidovudine but the lower doses usually used to treat rheumatic conditions have not been investigated.\(^5\) Spondarthropathies such as Reiter’s syndrome, psoriatic arthritis and ankylosing spondylitis, which are resistant to conventional disease-modifying anti-rheumatic drugs such as methotrexate, usually respond to TNF-\(\alpha\) blockade. TNF-\(\alpha\) blockers may even antagonize the enhancing effect of TNF-\(\alpha\) on HIV-replication. In some patients, TNF-\(\alpha\) inhibitors had to be discontinued because of infections but no deterioration of HIV disease was observed. Anti-TNF-\(\alpha\) agents may also be safely administered in the setting of hepatitis B and C virus co-infection.\(^3\),\(^6\)

Take home points
1. Autoimmune phenomena in terms of laboratory abnormalities without an associated rheumatic condition are highly prevalent in HIV-infected persons.
2. Bacterial, fungal or opportunistic pathogens may be recovered from virtually every structure of the musculoskeletal system.
3. The wide spectrum of articular complaints includes non-specific arthralgia, HIV-associated arthritis, Reiter’s syndrome and psoriatic arthritis.
4. Myopathic problems consist of rhabdomyolysis, polymyositis and zidovudine myopathy.
5. Vasculitis may present as cryoglobulinaemia, large vessel vasculitis, cerebral angiitis and polyarteritis nodosa, among other entities.
6. SLE has many features of HIV infection and may also induce false positive HIV serology.
7. Bones are subject to a high prevalence of osteonecrosis and osteoporosis, the latter of which is of multi-factorial origin and induces fractures. The contribution of HIV infection itself and ART to bone mineral loss is currently the focus of intense research.
8. Some rheumatic conditions require the use of immunosuppressive drugs.
References

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest


* An excellent overview of the rheumatic complications due to the immune reconstitution mediated by anti-retrovirals.


** A comprehensive review of the articular manifestations in HIV.


* An analysis of subjects developing granulomatous inflammation following HIV-infection.


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Renal complications have been associated with human immunodeficiency virus (HIV) infection since as early as 1984. Although the incidence of end-stage renal disease (ESRD) in patients with HIV basically plateaued between 1996 and 2005, the prevalence has roughly doubled as a result of improved survival in this patient population. Now that HIV-positive patients with access to combined anti-retroviral therapy (ART) are living longer, chronic diseases, including kidney disease, have become a major source of morbidity and mortality. Renal injury may be directly or indirectly related to viral infection, may be a side effect of ART or may be due to other co-morbid conditions. We will focus here on kidney disease thought to be mediated by the virus. Kidney disease needs to be screened for in this susceptible population, and a broad differential should be considered. Patients who develop ESRD and are well controlled virologically, should be referred for a renal transplant evaluation.

**Diagnosis/screening**

Patients with HIV are at risk for HIV-specific renal diseases like HIV-associated nephropathy (HIVAN), HIV-related immune complex disease (ICD) and thrombotic microangiopathy (TMA) as well as non HIV-related kidney diseases (Table 25.1). However, identifying which patients have renal disease and distinguishing renal diseases based on clinical scenarios remains difficult. One autopsy series detected evidence of renal pathology in 84% of subjects, although only 31.8% of the subjects met diagnostic criteria for chronic kidney disease (CKD). Although HIVAN occurs almost exclusively in people of African descent, within this group there are multiple other aetiologies of renal disease with one retrospective review demonstrating almost an equal prevalence of HIVAN (27%) and ICD (21%). An Italian study involving a predominantly (90%) Caucasian population not on ART at the time of biopsy, diagnosed HIVAN in only 12.3% and ICD in 54.8% of subjects.

Twenty-five per cent of patients with HIV also have hepatitis C virus (HCV) co-infection. Patients with HIV/HCV co-infection have nearly a 50% increased risk of CKD, 15% increased risk of proteinuria and a 64% increased risk of acute renal failure compared with HIV infection alone. Patients with HCV co-infection more frequently have membranoproliferative glomerulonephritis and cryoglobulinaemia, both of which were found to be associated with worse renal outcomes and death. As a result,
the presence of HCV infection is considered a ‘high-risk’ factor for the development of renal disease.\textsuperscript{9}

Screening for renal disease in these patients is important but challenging. Assessing renal function is difficult as cystatin C is elevated in this population,\textsuperscript{10} and although one study showed that the modification of diet in renal disease (MDRD) equation and 24-hour urinary creatinine appear to be reliable measurements, their study population was predominantly Caucasian males and so the findings may not be applicable to the HIV-infected population.\textsuperscript{11} A few studies have suggested that screening for persistent microalbuminuria may identify previously unrecognized kidney disease.\textsuperscript{4,12} The Infectious Disease Society of America has set forth guidelines (Table 25.2) for screening.\textsuperscript{9}

So far no clinical criteria have been able to successfully distinguish renal pathologies non-invasively. Biopsy series have shown significant overlap between different renal diseases in terms of proteinuria, creatinine level and immunosuppression.\textsuperscript{5} Atta et al. reviewed 107 renal biopsies performed in HIV-positive patients and found that the presence of nephrotic range proteinuria and low CD4 count were neither sensitive nor specific for the diagnosis of HIVAN.\textsuperscript{13} Autoantibodies are often elevated in HIV infection (Table 25.3), making serologies less useful.\textsuperscript{14} Given that clinical features overlap for many of these conditions and therapies may differ, it is recommended to consider a broad differential diagnosis and consider obtaining a renal biopsy in HIV-positive patients who develop renal failure.

**Table 25.1 Differential diagnosis for HIV-related nephropathy**

- HIV-associated nephropathy
- HIV-related immune complex disease (‘lupus-like’, IgA, membranous, membranoproliferative, fibrillary, immunotactoid or postinfectious glomerulonephritis)
- Thrombotic microangiopathy
- Membranous nephropathy
- Membranoproliferative (often associated with hepatitis C co-infection)
- Minimal change disease
- Classic focal segmental glomerulosclerosis
- Diabetic glomerulopathy
- Interstitial nephritis
- Drug nephrotoxicity
- Hypertensive nephrosclerosis
- Amyloidosis

**Acute kidney injury**

There is an increased incidence of acute kidney injury (AKI) in patients with HIV even in the post-ART era. Studies have shown an increased incidence of AKI in HIV patients compared with matched HIV-negative controls both in the inpatient setting\textsuperscript{15} and the outpatient ambulatory care setting.\textsuperscript{16} The development of AKI in the hospital was associated with an increased mortality rate and with risk factors like diabetes, CKD,
advanced age, the presence of liver disease and hepatitis co-infection.\textsuperscript{15} In the outpatient setting, a prospective cohort study showed an association between the development of AKI and the degree of immunosuppression (CD4 count <200), co-infection with hepatitis C, history of opportunistic infection or acquired immunodeficiency syndrome (AIDS) defining condition, use of ART, viral load >10000 and male sex.\textsuperscript{16} The aetiology of renal failure was attributed to intrinsic renal disease (46\%) due to ischaemic acute tubular necrosis or nephrotoxic drugs or to pre-renal acute renal failure (38\%) from volume depletion, sepsis or liver disease.\textsuperscript{16}

Table 25.3 Prevalence of positive autoantibodies in HIV-infected individuals

<table>
<thead>
<tr>
<th>Autoantibody test</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid factor</td>
<td>19–60</td>
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<tr>
<td>Anti-nuclear antibodies</td>
<td>0–23</td>
</tr>
<tr>
<td>Anti-cardiolipin antibodies</td>
<td>10–94</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>20–71</td>
</tr>
<tr>
<td>Anti-neutrophil cytoplasmic antibody</td>
<td>12–33</td>
</tr>
<tr>
<td>Anti-myeloperoxidase antibodies</td>
<td>0–25</td>
</tr>
<tr>
<td>Anti-proteinase 3 antibodies</td>
<td>0–7</td>
</tr>
<tr>
<td>Cryoglobulins</td>
<td>33</td>
</tr>
<tr>
<td>• Hepatitis C virus negative</td>
<td>17</td>
</tr>
<tr>
<td>• Hepatitis C virus positive</td>
<td>42</td>
</tr>
<tr>
<td>Anti-glomerular basement membrane</td>
<td>17</td>
</tr>
</tbody>
</table>

Reprinted by permission from Macmillan Publishers Ltd: Nature Clinical Practice Nephrology\textsuperscript{14} 2006.
**Chronic kidney disease**

Lucas et al. followed a large cohort of HIV-positive African Americans over 15 years and found an incidence of ESRD of 1% per year, which was a 10-fold higher risk than in the general African American population. Furthermore, a retrospective cohort study found that being HIV positive was an equivalent risk to diabetes for the development of ESRD in black patients. Although patients with HIV are at risk for developing a wide array of renal diseases, we will focus here on renal diseases where there is some evidence of a causal link between infection with HIV and the nephropathy.

**HIVAN**

The most common and well studied kidney disease associated with HIV infection is HIVAN, which occurs virtually exclusively in people of African descent. Recent genome-wide mapping identified an African ancestral locus in chromosome 22 that strongly predicted susceptibility to HIVAN and related renal diseases. Initially variants of MYH9 within the chromosome 22 locus were thought to account for this susceptibility, as there is a rare Mendelian renal disease caused by MYH9 mutations. However MYH9 polymorphisms were determined to be sentinels for closely linked variants in the neighbouring gene APOL1, which demonstrated a stronger link to renal disease. These APOL1 risk variants were likely positively selected for in African populations by conferring resistance to trypanosomiasis, or African sleeping sickness, endemic to Sub Saharan Africa. However the mechanism by which APOL1 variants contribute to HIVAN remains unknown. Nor has a role for MYH9 in affecting HIVAN susceptibility been excluded. The use of genetic testing to determine HIVAN susceptibility remains an ongoing area of debate.

Although case reports have documented the development of HIVAN in asymptomatic HIV infection or in acute HIV seroconversion, HIVAN occurs predominantly in patients with advanced, uncontrolled HIV disease. Clinical presentation usually involves a rapid progression of renal failure, proteinuria which may be in the nephrotic range, and large, echogenic kidneys on ultrasound. Patients tend to be normotensive and non-oedematous in contrast to other forms of glomerulonephritis. Classic HIVAN is characterized pathologically by focal segmental glomerulosclerosis with collapsing glomeruli, microcystic tubular dilatation, tubulo-interstitial inflammation and tubulo-recticular inclusions (TRIs), although these are non-specific and rarely seen in the post HAART era. There is also podocyte dysregulation in HIVAN characterized by podocyte dedifferentiation and proliferation.

HIVAN has been studied extensively and has been shown to be a result of viral gene expression in the kidney. HIV has been shown to infect renal glomerular and tubular epithelium. Even after successful treatment with ART demonstrated by an improvement in renal function and pathology, there is still detectable virus within the kidney suggesting that the kidney may be a reservoir for the virus.

**HIV-related immune complex kidney disease**

ICD has been less extensively studied than HIVAN. It encompasses a broad list of renal diseases, which may or may not be related to direct viral infection. HIV is often
associated with a polyclonal hypergammaglobulinaemia as well as with circulating immune complexes. These immune complexes consist mostly of IgA or IgG antibodies against viral antigens like p24 or gp120, and they may be passively trapped in the kidney or may form in situ immune complexes within the kidney. It has been proposed that this immune complex deposition leads to the development of glomerulonephritis. Patients with ICD usually present with hypertension, proteinuria, renal dysfunction, and an ‘active’ urine sediment with haematuria and/or red blood cell casts. Serum C3 levels may be normal or decreased. These disorders often share some histological findings with HIVAN including the presence of TRIs, podocyte hyperplasia, microcystic tubular dilatation, fibrocellular crescents and interstitial inflammation, which usually comprises B lymphocytes in ICD versus a predominantly T lymphocyte infiltrate in HIVAN.

There have been multiple case reports and case series describing patients with HIV who develop a ‘lupus-like’ glomerulonephritis. These patients develop pathology consistent with lupus but do not meet clinical or serological criteria for the diagnosis of systemic lupus erythematosus. Clinical findings usually include heavy proteinuria with a nephrotic syndrome, hypertension, microscopic haematuria and an elevated creatinine (usually >3.0 mg/dl). The pathological findings are consistent with lupus nephritis: a focal or diffuse proliferative glomerulonephritis or membranous nephropathy on light microscopy; immunofluorescence demonstrating a ‘full house’ pattern with staining for immunoglobulins (IgG, IgM, IgA) and complement (C1q and C3); ultrastructural findings of large subendothelial deposits (‘wire loops’). Effective treatment for these patients has not been well studied and, at least in the retrospective cohort of patients who presented with advanced disease, prognosis was poor with 10/14 patients progressing to end-stage renal disease within 1 year of biopsy.

IgA nephropathy has also been associated with HIV infection. These patients tend to have haematuria, an active urine sediment with red blood cell casts and proteinuria, which may or may not be in the nephrotic range. Kimmel et al. detected idiotypic IgA antibodies reacting with IgG and IgM antibodies against HIV p24 and gp120 antigens both in the circulation and in eluates from renal biopsies taken from two patients. Serum IgA levels lack specificity so are not helpful in making the diagnosis. There is no clear treatment strategy for the management of HIV-positive patients with IgA nephropathy because of a lack of data in this patient population.

**TMA**

TMA may be the most common microvascular injury associated with HIV infection, but it is less prevalent in the post-ART era. Patients with TMA tend to have more advanced HIV disease. HIV-associated TMA may present as either a thrombotic thrombocytopenic purpura (TTP) or a haemolytic uraemic syndrome (HUS) and does not differ clinically or pathologically from TMAs in HIV-negative patients. Renal dysfunction is usually manifested by haematuria, proteinuria and acute renal failure. Treatment of TMA in this patient population has not been rigorously studied, and case reports have shown inconsistent results with traditional therapies. One case series showed a higher incidence of death in patients with HIV-associated TMA compared with HIV-positive patients without TMA.
There is evidence to support that the pathogenesis of HIV-associated TMA is virally mediated. HIV p24 antigen has been identified in endothelial cells from a seropositive patient who developed TTP suggesting that the virus may be involved in endothelial damage, which is the hallmark of TMA. Further evidence for a pathogenic role of HIV in the development of TMA comes from an animal model of HIV-2 infected macaques. However, the specific role the virus may play in TMAs is still unknown.

**Treatment**

The 2005 IDSA guidelines outline recommendations for therapy in patients with HIVAN and non-HIVAN kidney disease (Table 25.4).

**ART**

The strongest evidence for treatment of HIV-associated kidney disease is for the use of ART in patients with HIVAN. A 12-year cohort study showed a 60% risk reduction in incident HIVAN associated with ART use, and no patients who were treated with ART before progressing to AIDS developed HIVAN. Another multi-centre cohort study showed a 76% risk reduction for progression to renal replacement therapy with ART use in subjects with biopsy-proven HIVAN. There have also been some case reports that have shown significant improvement in renal function both clinically and pathologically of HIVAN after treatment with ART.

Data in HIV-positive patients with non-HIVAN kidney disease are less consistent, but overall still favour ART use in patients with HIV and chronic kidney disease. Although a large, retrospective, multi-centre cohort study did not show any effect of ART on patients with non-HIVAN kidney disease, other studies that included HIV-positive patients with kidney disease of all aetiologies have shown an overall improvement in renal function, often with the greatest improvement seen in the group with the most severe renal dysfunction. The most recent renal dosing guide-

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**Table 25.4** Infectious Disease Society of America management recommendations for HIV-positive patients with evidence of renal disease

- Target blood pressure of 125/75 mm Hg or less using ACE inhibitors or ARBs as first-line agents for patients with proteinuria. Avoid calcium channel blockers in patients on protease inhibitors
- Dialysis and placement of dialysis access (preferably native arteriovenous fistula if haemodialysis) should not be withheld solely because of HIV infection
- Patients with HIVAN should be started on combined ART at diagnosis, and ART should not be withheld based on degree of renal dysfunction
- Renal transplant, performed at a centre experienced with transplanting HIV-positive patients, may be considered for a patient with ESRD
- If ART alone does not improve renal function in a patient with HIVAN, consider adding corticosteroids, ACE inhibitors or ARBs

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; ART, anti-retroviral therapy; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; HIVAN, human immunodeficiency virus-associated nephropathy.
lines may be found on the internet at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

**Steroids, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)**

Corticosteroids, ACE inhibitors and ARBs have been shown to improve renal outcomes in patients with HIVAN, but most of the studies were performed prior to the introduction of ART and so it is not clear what additional benefit, if any, is provided when adding these medications to ART.\(^ {43,44} \)

**Renal replacement therapy**

The 1-year survival of HIV-positive dialysis patients has improved from 56% in 1990 to 74% in 1999 based on the United States Renal Data System database, but the overall outcomes in patients with HIV are still inferior when compared with matched HIV-negative controls.\(^ {45} \) There does not appear to be any benefit of one mode of renal replacement therapy over another.\(^ {46} \)

**Transplant**

HIV-positive patients are successfully being transplanted at many institutions, and the survival rates are similar to HIV-negative transplant recipients with a 1- and 3-year patient survival of 94% and graft survival of 83%.\(^ {47} \) The patients must have well-controlled disease. There is a high rate of allograft rejection in this population, which is likely to be due to the impact of ART on the pharmacokinetics of immunosuppressants, but the overall allograft loss rate at 3 years is similar to the general transplant population.\(^ {47} \)

**Take home points**

1. HIV infection is associated with a broad list of renal pathologies including HIVAN, ICD and TMA.
2. HIVAN occurs predominantly in people of African descent with uncontrolled disease.
3. Clinical criteria alone are poor predictors of renal pathology; kidney biopsy remains the gold standard.
4. The presence of HIVAN is an indication for initiating ART regardless of CD4 count.
5. Well-controlled, HIV-positive patients with ESRD should be referred for renal transplant evaluation.

**References**

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest


**Identifies a risk allele associated with the development of focal segmental glomerulosclerosis and HIV-associated nephropathy.**


*Pathological description of HIV-associated nephropathy.*


**Confirms that HIV-associated nephropathy is a result of viral gene expression.**


*Demonstrates that the renal epithelium is infected in HIV-associated nephropathy and that the kidney is a viral compartment.*


* Shows a reduction in HIVAN incidence with the use of combined ART.


Chapter 26

NSAID nephrotoxicity

Wai Y. Tse and Dwomoa Adu

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed groups of drugs for the treatment of pain and inflammation. It is estimated that worldwide, more than 30 million people take NSAIDs daily. Although uncommon, the widespread use of NSAIDs means that renal complications are likely to be seen frequently.

Non-selective NSAIDs inhibit both constitutive cyclooxygenase-1 (COX-1) and inducible cyclooxygenase-2 (COX-2), the rate-limiting enzymes that are involved in production of prostaglandins and thromboxane $A_2$. It was hoped that COX-2 selective NSAIDs would have anti-inflammatory activity but lack the deleterious gastrointestinal, renal and cardiovascular effects on homeostatic functions mediated by COX-1 activation. However, in the kidney, COX-2 is constitutively expressed and is highly regulated in response to alterations in intravascular volume. In addition to their role in inflammation, prostaglandins are also important regulators of vascular tone, salt and water balance, and renin release. Thus, renal adverse effects such as salt and water retention, hypertension, acute tubular necrosis, acute interstitial nephritis, hyperkalaemia, acute and chronic renal failure are associated with non-selective, as well as COX-2 selective NSAIDs.

COX-2 inhibitors

Three highly selective COX-2 NSAIDs were originally approved by the US Food and Drug Administration (FDA): namely, celecoxib, rofecoxib and valdecoxib. However, increased myocardial infarction and ischaemic strokes seen with rofecoxib led to its withdrawal in 2004. In 2005, the FDA advisory committee concluded that COX-2 inhibitors increase the risk of cardiovascular events and recommended the suspension of valdecoxib. Celecoxib was allowed to remain in the marketplace, but with a black box warning indicating a risk of adverse cardiovascular events. The European Medicine Agency also issued the recommendation that selective COX-2 inhibitors be considered contraindicated in patients with ischaemic heart disease and/or stroke, that they should be avoided in patients with risk factors for coronary heart disease, and that all patients take the lowest effective dose for the shortest time necessary to control symptoms.

Low-dose aspirin irreversibly inhibits platelet COX-1 thereby blocking the synthesis of thromboxane $A_2$, a prothrombotic factor and has little effect on endothelial COX-2 derived prostacyclin. Prostacyclin inhibits platelet aggregation and leads to vasodilatation.
Due to its selectivity, low-dose aspirin is the drug of choice for the prevention of thrombotic events, even for those patients with underlying renal disease, without the risk of jeopardizing prostaglandin-dependent renal function. By contrast, higher doses of aspirin can also inhibit COX-2-derived prostacyclin production. Vascular prostacyclin is mainly COX-2-derived and is inhibited by both non-selective NSAIDs and COX-2 selective NSAIDs. Therefore, a potential cardiovascular risk is seen with non-selective NSAIDs as well as COX-2 selective drugs.4

**COX in the kidney**

Prostaglandins are unsaturated fatty acid compounds synthesized from cell membrane phospholipids. The enzyme phospholipase A2 converts phospholipids into arachidonic acid, which is the substrate for three different enzymes: COX, which is inhibited by NSAIDs, cytochrome P-450 mono-oxygenase, and lipoxygenase (Fig. 26.1). Phospholipase A2 is activated by kinins, vasopressin, angiotensin II and extracellular hypersmolarity and increases prostaglandin synthesis through the three pathways.5 Each pathway influences some aspects of renal haemodynamics or tubular function. The blockade of COX by NSAIDs increases the substrate available to the other two pathways leading thus to possible adverse renal effects.

Two isoforms of COX (COX-1 and COX-2) have been identified in mammalian cells. COX-1, which is constitutively expressed, mediates gastric cytoprotection and vascular homeostasis.6 COX-2 expression is regulated by salt and water intake, medullary tonicity,

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**Fig. 26.1** The pathway of arachidonic acid metabolism. The lipoxygenase pathway results in the production of leukotrienes; the role of these compounds in the kidney is unclear. The cyclo-oxygenase pathways leads to the production of the unstable cyclic endoperoxidase PGG2. Subsequent enzymatic conversion results in the production of the classical 2 series prostaglandins PGI2, PGE2, PGD2, PGF2α and thromboxane A2.
growth factors, cytokines and adrenal steroids, and produces prostaglandins in inflamed tissues. Selective blockade of pain and inflammation mediated by COX-2 stimulation without deleterious effects on homeostatic functions mediated by COX-1 activation should be useful.

Constitutive COX-2 mRNA as well as inducible COX-2 mRNA are present in the kidney. In the human kidney, COX-2 is present in podocytes, endothelium, proximal convoluted tubule and collecting duct, renal vasculature, the macula densa, and the medullary interstitial cells of the kidney, whereas COX-1 is found in the vasculature, the collecting ducts, glomeruli and medullary interstitial cells. It remains to be seen which of the two isoforms present in the vasculature is the predominant source of the increased production of vasodilator prostaglandins that is critical to the preservation of renal blood flow when there is volume depletion. Inhibition of this homeostatic response accounts indeed for the most common renal side effects associated with non-selective NSAID therapy. Many of the other renal effects of non-selective anti-inflammatory drugs (including sodium retention, decreased glomerular filtration rate and effects on renin–angiotensin levels) appear mediated by the inhibition of COX-2 rather than COX-1.

COX-2-dependent prostaglandin formation is also necessary for normal renal development. In mice, the complete absence of COX-2 resulted in severe renal dysplasia characterized by a postnatal arrest of maturation in the subcapsular nephrogenic zone and progressive deterioration with increasing age. Antenatal exposure of both mice and rats to an inhibitor of COX-2, but not of COX-1, had similar effects. In contrast, disruption of COX-1 gene expression failed to influence nephrogenesis.

**Actions of renal prostaglandins**

The kidney produces the vasodilator prostaglandins PGE$_2$, PGF$_2\alpha$ and PGI$_2$ and the vasoconstrictor thromboxane A$_2$. These autacoids, synthesized and metabolized by the kidney, autoregulate renal blood flow, renin release, tubular ion transport and water metabolism (Table 26.1). PGI$_2$, which is mainly present in the afferent arteriole and glomerulus, plays a major role in controlling glomerular haemodynamics. In contrast, PGE$_2$, predominantly produced in the collecting tubule and within the interstitium, regulates medullary haemodynamics.

**Effects of COX-2 NSAIDs on renal prostaglandins**

The urinary excretion of PGE$_2$ and 6-keto-PGF$_{1\alpha}$, the stable metabolite of PGI$_2$, reflects the renal synthesis of PGE$_2$ and PGI$_2$ respectively. In healthy older adults, rofecoxib reduced baseline urinary 6-keto-PGF$_{1\alpha}$ by 47%, and this was comparable to the 53% reduction induced by indomethacin. In another study, rofecoxib reduced urinary PGE$_2$ and 6-keto-PGF$_{1\alpha}$ excretion in healthy volunteers by approximately 40–50%, similar to that induced by meloxicam or diclofenac. Further, excretion of urinary 6-keto-PGF$_{1\alpha}$ was comparable in response to celecoxib and traditional NSAIDs. In a trial of healthy elderly volunteers on a normal sodium intake, multiple doses of twice-daily celecoxib reduced PGE$_2$ and 6-keto-PGF$_{1\alpha}$ excretion to the same degree as naproxen by approximately 65% and 80% respectively. These data suggest that the COX-2
 isoform plays an important role in renal prostaglandin biosynthesis. It is thus likely that COX-2 inhibitors will impact on renal function as do non-selective NSAIDs.

**Maintenance of renal blood flow and glomerular filtration rate**

Prostaglandins maintain renal blood flow and glomerular filtration rate despite vasoconstrictor stimuli such as leukotrienes, thromboxane A$_2$, angiotensin II, vasopressin, endothelin and catecholamines. Catecholamines also stimulate the local production of prostaglandins, resulting in a feedback loop between vasoconstrictors and vasodilatory prostaglandins. PGF$_{2\alpha}$-like peroxidation products also have major vasoconstrictive effects. Thus, in patients with underlying ischaemic or inflammatory renal injury, the addition of non-selective or COX-2 selective NSAID not only decreases the production of vasodilatory prostaglandins, but also results in the non-enzymatic formation of vasoconstrictor metabolites of arachidonic acid, which further jeopardize renal blood flow and glomerular filtration. Under normal euvoaemic conditions, NSAIDs produce negligible effects on renal haemodynamics. However, in the presence of salt depletion or an ineffective circulating plasma volume or in conditions characterized by high circulating levels of vasoconstrictor hormones, NSAIDs may be nephrotoxic. Such conditions include cirrhosis, hypovolaemia, cardiac disease, renal disease, septic shock, advanced age, diuretic use, diabetes mellitus and after surgery.

In elderly salt-replete subjects, both indomethacin and rofecoxib decreased sodium excretion but only indomethacin reduced glomerular filtration rate. Celecoxib, like

<table>
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<th>Table 26.1 Effects of renal autocoids in the kidney</th>
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<tbody>
<tr>
<td><strong>Site of action</strong></td>
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<tr>
<td>PgI$_2$</td>
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<tr>
<td>Afferent arteriole</td>
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<td>Efferent arteriole</td>
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<tr>
<td>Capillary tuft</td>
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<tr>
<td>Glomerular mesangium</td>
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<tr>
<td>Juxtaglomerular apparatus</td>
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<tr>
<td>PGE$_2$</td>
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<tr>
<td>Glomerular mesangium</td>
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<tr>
<td>Thick ascending loop of Henle</td>
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<tr>
<td>Collecting tubule, interstitium and vasa recta</td>
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<tr>
<td>PGG$_2$</td>
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<tr>
<td>PGH$_2$</td>
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<tr>
<td>Thromboxane</td>
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<td>Intrarenal arterioles</td>
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rofecoxib, affects renal function in selected groups of subjects at risk of NSAID-related renal effects. Whelton et al. compared celecoxib with naproxen in 29 healthy elderly subjects in a single blind, randomised, cross-over study. Subjects were given either celecoxib 200 mg twice daily for 5 days followed by celecoxib 400 mg twice daily for the next 5 days, or they received naproxen, 500 mg twice daily for 10 days. After a 7-day washout, subjects were crossed over to the other regime. Glomerular filtration rate fell more with naproxen than with celecoxib, although urinary excretion of prostaglandin E₂ and 6-keto-PGF₁α and sodium excretion was comparable. In another study involving salt-depleted elderly subjects, rofecoxib and indomethacin induced a comparable reduction of glomerular filtration rate. These studies illustrate that COX-2 inhibitors and non-selective NSAIDs have similar effects on renal haemodynamics.

Renin release and potassium homeostasis

PGE₂, PGI₂ and arachidonic acid are potent stimuli of renin release. Both non-selective and COX-2 selective NSAIDs can inhibit renin secretion, and under some circumstances lead to hyporeninaemia and hypoaldosteronism with an attendant hyperkalaemia. This is particularly common in patients with pre-existing renal impairment. Inhibition of prostaglandin synthesis can also lead to hyperkalaemia by decreasing distal tubular flow rate and sodium delivery, both of which limit potassium secretion.

Effects of COX-2 inhibitors on renin release

In the mammalian kidney, the macula densa is involved in regulating afferent arteriolar tone and renin release by sensing alterations in luminal chloride via changes in the rate of sodium/potassium/chloride co-transport. Studies using animals have indicated that selective COX-2 inhibitors can significantly decrease plasma renin levels, and mRNA expression under certain high renin states. There is evidence that COX-2 expression in the renal cortex is inhibited by angiotensin II and stimulated under conditions of low sodium intake or diuretic administration. Randomized cross-over studies in healthy humans who were administered frusemide and/or a low-sodium diet demonstrated inhibition of renin release by the COX-2 inhibitor rofecoxib and meloxicam. Enhanced COX-2 expression has been demonstrated in the macula densa of patients with Bartter’s syndrome, a disorder of impaired sodium chloride absorption in the thick ascending loop of Henle. In addition, patients with hyperprostaglandin E syndrome and antenatal Bartter’s syndrome, who have genetic abnormalities in thick limb/macula densa sodium chloride reabsorption, rofecoxib administration suppressed hyperreninemia as effectively as indomethacin, further supporting a role for COX-2 metabolites in mediation of renin release.

If the activity of the renin–angiotensin system is diminished or insufficient to maintain electrolyte balance, then, at least in some circumstances, increased COX-2 expression and synthesis of prostaglandins activate expression and release of renin, leading to increased activity of angiotensin II and aldosterone, facilitating re-establishment of intravascular volume homeostasis. Once this is achieved, the expression of COX-2 is reduced through inhibition by angiotensin II, decreasing a stimulus for renin production and release.
Natriuresis and diuresis

Renal prostaglandins are natriuretic and diuretic. They inhibit sodium and chloride reabsorption in the proximal and distal nephron and in the loop of Henle, reduce renal cortico-medullary solute gradient and antagonize the action of vasopressin in vivo. Although prostaglandins acutely influence salt and water excretion, they do not regulate it under normal conditions.

Conditions in which renal prostaglandins are important (Table 26.2)

Under normal euvolaemic conditions, NSAIDs produce negligible effects on renal haemodynamics. However, in the presence of salt depletion, of an ineffective circulating plasma volume, or of conditions characterized by high circulating levels of vasoconstrictor hormones, NSAIDs may be nephrotoxic. Such conditions include cirrhosis, hypovolaemia, cardiac disease, renal disease, septic shock, advanced age, diuretic use and post surgery.

Table 26.2 Conditions that predispose to NSAIDs-induced renal failure

<table>
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<th>Conditions</th>
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<tr>
<td>Hypovolaemia</td>
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<td>Haemorrhage</td>
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<td>Septic shock</td>
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<td>Congestive cardiac failure/Heart disease</td>
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<td>Nephrotic syndrome</td>
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<td>Cirrhosis with ascites</td>
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<tr>
<td>Anaesthesia/Surgery</td>
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<tr>
<td>Pre-eclampsia</td>
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<tr>
<td>Sodium depletion: Diuretics</td>
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<tr>
<td>Gastrointestinal losses</td>
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<tr>
<td>Renal artery stenosis</td>
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<tr>
<td>Glomerulonephritis</td>
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<td>Urinary tract obstruction</td>
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<td>Toxic injury: Cyclosporin A</td>
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<tr>
<td>Tacrolimus</td>
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<tr>
<td>Gentamicin</td>
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<tr>
<td>Urinary tract infection</td>
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<tr>
<td>Hypercalcaemia</td>
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<tr>
<td>Advancing age</td>
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<td>Chronic renal failure</td>
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Clinical syndromes associated with non-selective and COX-2 selective NSAIDs

Acute renal impairment/acute tubular necrosis

In circumstances where there is poor renal perfusion with high renin levels, non-selective and COX-2 selective NSAIDs can reduce glomerular filtration rate resulting in acute renal failure. This complication has been reported with most NSAIDs but only rarely with aspirin. Renal failure has also been described after topical and intramuscular NSAIDs.  

A multi-centre study in France examined the incidence and subsequent outcome of patients with drug-induced acute renal failure. Of the 398 patients with acute renal failure, 147 (36.9%) had taken NSAIDs. A third required dialysis and 71.4% recovered or regained previous renal function. A renal biopsy obtained in 25 patients with NSAID-associated renal failure disclosed acute tubular necrosis and acute interstitial nephritis in 21 patients and either minimal change nephropathy or chronic renal damage in four. A nested case–control study using the United Kingdom General Practice Research Database reported that current users had a relative risk of developing acute renal failure of 3.2 (95% CI 1.8–5.8) compared with non-NSAID use. This increased risk was higher in patients with heart failure, hypertension and diabetes. Thus, although renal side effects from NSAIDs use are relatively rare, renal damage can be irreversible and outcome can be fatal. Renal function usually improves on drug withdrawal, although in some cases permanent renal damage may ensue. 

Acute renal failure and hyperkalaemia have been observed after the administration of COX-2-selective inhibitors to patients with risk factors for NSAID-induced acute renal insufficiency, including underlying chronic renal impairment and volume depletion. Acute renal failure has also been reported in a patient with a renal transplant 4 weeks after starting rofecoxib. 

Renal dysfunction with COX-2 inhibitors

In one study, renal adverse events were reported in 24.3% of 144 patients receiving celecoxib and 30.8% of 143 patients receiving diclofenac and omeprazole. Renal failure (defined as a rise in serum creatinine to above 200 μmol/l) was seen in 5.6% and 6.3% of patients respectively. Overall, renal adverse events were more common in patients with renal impairment (celecoxib: 51.4% and diclofenac plus omeprazole: 40.7%). In another study comparing rofecoxib and naproxen, the incidence of adverse effects related to renal function was low and similar in the two groups (1.2% in the rofecoxib group and 0.9% in the naproxen group). In a review of randomized clinical trials lasting 2 weeks or more involving celecoxib, a rise in serum creatinine was seen in 0.7% of patients treated with celecoxib and 1.2% of patients treated with diclofenac (p<0.05). In a meta-analysis of data from company clinical trial reports, there was no difference in the incidence of renal adverse events (defined as an increase in serum creatinine >1.3 times the upper limit of normal) in 15319 patients treated with celecoxib (0.3%) or other NSAIDS (0.5%), relative risk 0.78 (95% CI 0.48–1.3).
A retrospective nested case–control study in the United States Department of Veterans Affairs health care system included 1459721 new NSAID users and found that the risk of acute kidney injury may be lower with more COX-2 selective NSAIDs. On the other hand, several hundred cases of acute renal failure associated with celecoxib or rofecoxib have been reported to the FDA. The majority of these patients had additional risk factor for acute renal failure including chronic kidney disease, congestive heart failure, hypertension or diuretic use. In summary, renal side effects occur with COX-2 selective inhibitors and non-selective inhibitors. Caution must be exercised with their use in elderly patients with comorbidities or those who have other risk factors for acute renal failure.

Postoperative use of NSAIDs

A meta-analysis of 19 trials showed that the post-operative use of NSAIDs in adults with normal pre-operative renal function resulted in a 16 ml/min fall of creatinine clearance on the first day after surgery as compared with placebo. No cases of post-operative acute renal failure requiring dialysis were seen. The conclusions were that NSAIDs caused a clinically unimportant reduction in renal function in the early post-operative period in patients with normal renal function and that these drugs should not be withheld in such patients. However, others have reported an overall incidence of postoperative renal insufficiency of 18% after major surgery, with a subsequent hospital mortality rate of 13%.

Acute tubulo-interstitial nephritis

NSAIDs of different chemical classes have been associated with acute tubulo-interstitial nephritis and renal failure. Acute allergic tubulo-interstitial nephritis due to NSAIDs is much less common than haemodynamic renal failure. The patients are often elderly and the drug may have been taken for months or years before the development of acute interstitial nephritis. Clinical evidence of an allergic reaction; such as fever, rash, arthralgia, eosinophilia, and eosinophiluria is uncommon. Of note, proteinuria, often in the nephrotic range, may occasionally appear, especially in fenoprofen-induced tubulo-interstitial nephritis. Cases of interstitial nephritis have been reported with both celecoxib and rofecoxib. In two cases, interstitial nephritis was associated with glomerulopathies; one case with minimal change disease and the other one with membranous nephropathy. Thus, there is little evidence that suggest a major difference between NSAIDs and COX-2 inhibitors in the incidence of acute interstitial nephritis.

NSAID-induced acute and chronic tubulo-interstitial nephritis is formally diagnosed by renal biopsy. A patchy acute tubular damage co-exists with tubulo-interstitial infiltrate predominantly of T lymphocytes and, to a lesser extent of monocytes/macrophages, B lymphocytes, plasma cells and eosinophils. Rarely, a granulomatous interstitial nephritis is seen. Immunofluorescence microscopy is usually negative or non-specific. The predominance of T lymphocytes in the interstitial infiltrate has been taken to indicate that T lymphocyte activation mediates this syndrome, rather than a humoral mechanism as in other forms of drug-induced acute interstitial nephritis. Inhibition of renal COX has also been incriminated in the genesis of NSAID-induced acute
tubulo-interstitial nephritis. The resulting stimulation of the lipoxygenase pathway of arachidonic acid metabolism produces leukotrienes, which are potent chemotactic factors for lymphocytes. Prostaglandins also have immunomodulatory functions, the inhibition of which might lead to an escape from immunological control. Inhibition of prostaglandins indeed leads to sustained or enhanced expression of proinflammatory and profibrogenic mediators, with eventual tubulo-interstitial damage and fibrosis.

In addition to renal failure, hyperchloraemic acidosis has been consistently noted, together with impaired concentrating ability, which last for many months despite recovery of renal function after the acute episode. Renal failure may occasionally necessitate dialysis. After drug withdrawal, renal failure and proteinuria usually resolve, although this may take up to a year or may be only partial, with chronic interstitial fibrosis progressing to chronic renal failure. Prednisolone has been successfully used in anecdotal reports without conclusive evidence that corticosteroids hasten the resolution of the renal lesion.

Still, the fact that experimental acute interstitial nephritis typically precedes fibrogenesis by as short a time as 7–14 days, taken together with the potential for incomplete resolution leads us to advocate a 1-month course of prednisolone; starting at a dose of 30 mg daily, to be rapidly reduced as renal function improves. Although cross-reactivity among NSAIDs remains unknown, it is wise to avoid other NSAIDs in patients who have developed NSAID-induced acute interstitial nephritis. If impossible, a compound from a different structural class should be selected and the patient should be monitored closely.

**Glomerulonephritis and vasculitis**

Membranous nephropathy with nephrotic syndrome may occur as idiosyncratic reaction to various classes of NSAIDs. The temporal association with the intake of NSAIDs, the prompt and complete recovery after drug discontinuation, and the absence of recurrent disease may help distinguish NSAID-associated membranous nephropathy from the idiopathic form. As with NSAIDs, glomerulopathies with the nephrotic syndrome can occur with COX-2 inhibitors. Membranous nephropathy associated with etodolac, a selective COX-2 inhibitor, and membranous nephropathy with acute interstitial nephritis secondary to celecoxib have been described.

Anecdotal reports of generalized vasculitis and glomerulonephritis in patients given NSAIDs include both thrombotic and non-thrombotic thrombocytopaenic purpura, and vasculitis. It is difficult to be certain of a causal relationship with NSAIDs in many of these cases, but generalized vasculitis has been reported after re-challenge with piroxicam.

**Renal papillary necrosis**

Renal papillary necrosis has been infrequently reported in patients treated with ibuprofen, indomethacin, phenylbutazone, fenoprofen and mefenamic acid. One case of celecoxib-related renal papillary necrosis has been reported.

**Chronic renal failure**

Sandler et al. evaluated the risk for chronic renal disease associated with regular use of non-aspirin NSAIDs in 554 patients with newly diagnosed chronic renal dysfunction.
They found a twofold increased risk for chronic renal disease in patients with a history of previous daily use of NSAIDs (adjusted odds ratio 2.1; 95% CI 1.1–4.1). The increased risk was predominantly limited to men older than 65 years, for whom the odds ratio was 10.0 (95% CI 1.2–82.7) after adjusting for use of other analgesics. The NSAID-associated risk was also greater among those with a history of conditions that might indicate an enhanced susceptibility to the effects of NSAIDs, including previous myocardial infarction, congestive heart failure, heavy alcohol consumption (as a surrogate for cirrhosis) or diuretic use. These observations were confirmed in a recent case–control study of 716 patients with end-stage renal failure and 361 controls. In this study, a high cumulative intake of NSAIDs (>5000 tablets) was associated with a 4.5-fold excess risk of end-stage renal failure, although the confidence interval was wide (1.0–19.5) and curiously this excess risk was not seen when average annual intake of NSAIDs was examined. However, other studies of NSAID usage in hospitalized patients and also cohort studies did not show this association. The reasons for these discrepant findings are unclear. Some patients with chronic renal failure rely on prostaglandin-mediated vasodilatation to maintain renal blood flow. Addition of NSAIDs may further deteriorate renal function. On balance, it seems likely that chronic usage of NSAIDs may be associated with a slightly increased risk for the development of chronic renal failure.

Salt and water retention
Non-selective NSAIDs have been reported to induce peripheral oedema in up to 5% of the general population. NSAID therapy may aggravate the sodium retention induced by renal hypoperfusion in heart failure, cirrhosis or the nephrotic syndrome. Hyponatraemia may occur if water retention is disproportionate to sodium retention, especially when thiazide diuretics are given simultaneously. Medullary PGE₂ plays an important role in regulating sodium chloride and water reabsorption in the medullary thick ascending limb and collecting duct. COX-1-derived prostaglandins from cortical and medullary collecting ducts are hypothesized to be involved in the natriuretic response and sodium retention. In a rat model of cirrhosis and ascites, a COX-1 selective inhibitor but not a COX-2 selective inhibitor decreased sodium excretion and impaired the diuretic and natriuretic responses to frusemide.

Hypertension
It is established that a 2 mmHg reduction in diastolic blood pressure results in about a 40% reduction in the rate of stroke and a 25% reduction in the rate of myocardial infarction. Two large meta-analyses encompassing more than 90 studies demonstrate that NSAIDs may increase blood pressure, especially in previously hypertensive patients. NSAIDs elevate supine mean blood pressure by 5 mmHg, a rise known to increase hypertension-related morbidity and mortality. This complication is of importance in the elderly who are frequently prescribed NSAIDs for musculoskeletal disorders and also have a high prevalence of other chronic disorders, including hypertension.

The two large trials that investigated the safety of COX-2 inhibitors, the Celecoxib Long-term Arthritis Safety Study (CLASS; Celecoxib) and Vioxx Gastrointestinal
Outcome Study (VIGOR; Rofecoxib), both found evidence for increased blood pressure in a minority of subjects.\textsuperscript{45,98} Whelton et al. performed a post hoc analysis on the renal safety of celecoxib, incorporating more than 50 clinical studies with more than 13000 subjects.\textsuperscript{21} The most common events, peripheral oedema (2.1%), hypertension (0.8%) and exacerbation of pre-existing hypertension (0.6%), were not dose- or time-related. Their incidence and profile were similar to those of non-selective NSAIDs. A similar post hoc analysis of rofecoxib revealed peripheral oedema in 3.8% of patients.\textsuperscript{11} Whelton et al. also compared the effects of celecoxib 200 mg and rofecoxib 25 mg over a 6-week period in 810 hypertensive patients with osteoarthritis, aged over 65 years.\textsuperscript{99} Oedema developed in nearly twice as many rofecoxib-treated than celecoxib-treated patients (9.5\% versus 4.9\%, \(p=0.014\)). Systolic blood pressure increased significantly in 17\% of rofecoxib, compared with 11\% of celecoxib-treated patients (\(p=0.032\)). In conclusion, celecoxib induced less frequently oedema and less rises in blood pressure than rofecoxib. A meta-analysis of COX-2 inhibitors and their effects on blood pressure showed that they were associated with a non-significantly higher relative risk of causing hypertension when compared with placebo (relative risk of 1.61; 95\% CI 0.91–2.84) or non-selective NSAIDs (relative risk of 1.25; 95\% CI 0.87–1.78).\textsuperscript{100+}

Several factors may explain the effects on blood pressure, including alterations in the renin–angiotensin pathway, changes in sodium and water retention by the kidneys, inhibition of vasodilating prostaglandins, and production of various vasoconstricting factors, including endothelin-1 and P450-mediated metabolites of arachidonic acid. There is evidence that intra-renal COX-2 activity protect against the development of hypertension during high salt intake. Selective intramedullary infusion of a COX-2 inhibitor or COX-2 antisense oligonucleotides caused animals to develop hypertension when they were placed on a high salt diet.\textsuperscript{101,102} As renal medullary COX-2 is expressed primarily in medullary interstitial cells,\textsuperscript{101} these studies suggest a critical role for the medullary interstitial cell in maintaining systemic blood pressure. Renal medullary interstitial cells produce significant amounts of PGE\(_2\), which can exert a dilating effect on vasa rectae,\textsuperscript{103} and inhibit salt absorption by the thick ascending limb and collecting ducts via basolateral PGE\(_2\) receptors.\textsuperscript{104} It may be that increased salt intake augments renal medullary interstitial cell COX-2 expression and PGE\(_2\) production, thereby promoting increased renal salt excretion and maintaining normal total body sodium content via a physiological feedback system. Thus, both non-selective NSAIDs and COX-2 inhibitors can raise blood pressure especially in hypertensive, elderly patients and there is no substantial evidence to suggest that COX-2 inhibitors are safer in this respect.

**Hyperkalaemia and hyporeninaemic hypoaldosteronism**

NSAIDs may cause hyperkalaemia and this is seen more commonly in patients with chronic renal failure, diabetes mellitus and type IV tubular acidosis through previously outlined mechanisms.\textsuperscript{87,105,106} Increases in potassium levels also occur with COX-2 inhibitors.\textsuperscript{107} NSAIDs must be used with caution in patients taking other drugs known to decrease renal potassium excretion, such as potassium-sparing diuretics, angiotensin converting enzyme inhibitors and β-blockers.
**Therapeutic use of NSAIDs in nephrotic syndrome**

NSAIDs reduce proteinuria in patients with the nephrotic syndrome, probably by reducing renal blood flow and glomerular filtration rate. The occurrence of irreversible renal failure in patients with a nephrotic syndrome treated with NSAIDs suggests great caution in the use of these drugs in patients with a nephrotic syndrome.

**Conclusion**

The increasing use of NSAIDs both from prescription and from over-the-counter sales will increase the prevalence of nephrotoxicity. A history of NSAID use should be sought in all patients with unexplained impairment of renal function and or proteinuria. In patients with volume depletion or decreased organ perfusion, the use of NSAIDs should be avoided. NSAIDs should not be prescribed in patients with chronic renal impairment, or with a functioning renal transplant. Patients with an NSAID-induced interstitial nephritis or papillary necrosis should not be given NSAIDs again. In some individuals who have developed NSAID-induced acute renal failure and who have recovered renal function, NSAIDs may be reintroduced if clinically necessary, provided that the risk factors for enhanced susceptibility have been corrected and that renal function is closely monitored.

COX-2, constitutively expressed in renal tissues, is involved in prostaglandin-dependent homeostatic processes. Administration of COX-2-selective inhibitors produce qualitative changes in urinary prostaglandin excretion, glomerular filtration rate, sodium retention and peripheral oedema, similar to those associated with non-selective NSAIDs. Their use requires, therefore, the same precautions as with traditional NSAIDs.

**Take home points**

1. Although uncommon, the widespread use of NSAIDs means that renal complications are likely to be seen frequently.
2. Two isoforms of COX (COX-1 and COX-2) have been identified in mammalian cells. COX-1, which is constitutively expressed, mediates gastric cytoprotection and vascular homeostasis. COX-2 expression is regulated by salt and water intake, medullary tonicity, growth factors, cytokines and adrenal steroids and produces prostaglandins in inflamed tissues.
3. Constitutive COX-2 mRNA, as well as inducible COX-2 mRNA, is present in the kidney.
4. In circumstances where there is poor renal perfusion with high renin levels, non-selective and COX-2 selective NSAIDs can reduce glomerular filtration rate resulting in acute renal failure.
5. Acute renal failure and hyperkalaemia have been observed after the administration of COX-2 selective inhibitors to patients with risk factors for NSAID-induced acute renal insufficiency.
6. NSAIDs of different chemical classes have been associated with acute tubulo-interstitial nephritis and renal failure.
7. On balance, it seems likely that chronic usage of NSAIDs may be associated with a slightly increased risk for the development of chronic renal failure.

8. Both non-selective NSAIDs and COX-2 inhibitors can raise blood pressure especially in hypertensive, elderly patients and there is no substantial evidence to suggest that COX-2 inhibitors are safer in this respect.

References

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest


** A review article of the side effects of non-steroidal anti-inflammatory drugs.


* A review article of the impact of non-steroidal anti-inflammatory drugs on renal prostaglandin production and their effects on renal blood flow and glomerular filtration rate.


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*** A review article of renal complications associated with non-steroidal anti-inflammatory drug use. Guidelines for use of non-steroidal anti-inflammatory drugs, detection of patients at risk and therapeutic approaches are provided.


* A prospective multi-centre study in France examining the incidence and subsequent outcome of patients with drug-induced acute renal failure.


* A retrospective nested case study from the USA showing that the risk of acute kidney injury may be lower with more selective non-steroidal anti-inflammatory drugs.


** A review article of renal complications associated with non-steroidal anti-inflammatory drug use.


REFERENCES

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<th>Page</th>
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**A review article of renal complications associated with non-steroidal anti-inflammatory drug use.**


* A meta-analysis of 54 studies showing the effects of non-steroidal anti-inflammatory drugs on blood pressure.


Chapter 27

Nephrotoxicity of drugs used in rheumatology: Analgesic nephropathy

Marc E. De Broe

Introduction

For patients with a chronic painful condition, regular ingestion of analgesics is normal. However, these drugs may have a nephrotoxic effect, and renal damage/failure may occur after some time in a poorly defined number of these patients.

Chronic analgesic nephropathy (AN) is a form of renal disease characterized by renal papillary necrosis and chronic interstitial nephritis caused by prolonged and excessive consumption of analgesic mixtures. It is invariably caused by compound analgesic mixtures containing aspirin or antipyrin in combination with phenacetin, paracetamol or salicylamide and caffeine or codeine in popular ‘over-the-counter’ proprietary mixtures.\(^1\),\(^2\)\(^*\)\(^\*\)

Diagnosis

The renal manifestations of analgesic nephropathy are usually non-specific: slowly progressive chronic renal failure, with urinalysis that may be normal or may reveal sterile pyuria and a mild proteinuria (less than 1.5 g/day).\(^3\),\(^4\) Hypertension and anaemia are commonly seen with moderate to advanced disease; more prominent proteinuria that can exceed 3.5 g/day can also occur at this time, a probable reflection of secondary haemodynamically mediated glomerular injury.

Most patients have no symptoms referable to the urinary tract, although flank pain or macroscopic/microscopic haematuria from a sloughed or obstructing papilla may occur or as a result of transitional cell carcinoma. Urinary tract infection is also somewhat more common in women with this disorder.

Despite the non-specific nature of the renal presentation, there are frequently other findings that point toward the presence of analgesic nephropathy.\(^3\),\(^4\) Most patients are between the ages of 30 and 70. Careful questioning often reveals a history of chronic headaches or low back pain that leads to the analgesic use. Also common are other somatic complaints (such as malaise and weakness), and ulcer-like symptoms or a history of peptic ulcer disease due in part to concomitant chronic non-steroidal anti-inflammatory drug (NSAID) ingestion.
Confirmation of the diagnosis requires a history of analgesic ingestion, often difficult to obtain. This can often be achieved by indirect questioning of the patient. The use of a book, containing colour photographs of the most frequently sold/used analgesics, is helpful.

This lack of reliable criteria and the high prevalence of analgesic nephropathy in the 1980s in Belgium (17.9% in 1984) led us to perform three prospective, multi-centre, controlled studies to define and validate diagnostic criteria for this disease. In the first study, all 273 patients at 13 Belgian dialysis centres who entered the dialysis programme were divided into case patients and controls. Case patients consisted of 85 patients who were found to have a history of analgesic abuse on the basis of an interview, a medical-chart analysis and review of additional information provided by the patients’ nephrologists. The interview focused on the use of medications for the relief of symptoms such as headache and joint pain. To help identify the medications they used, the patients were shown a book containing colour photographs of the 12 most frequently sold analgesics in Belgium. Analgesic abuse was defined as daily use of analgesics for at least 5 years, for a minimum total dose of 3000 units (one unit = one tablet or one dose of powder). The controls consisted of all 188 other patients with no history of analgesic abuse. Findings of a decrease in the lengths of the kidneys, irregular (‘bumpy’) contours, and papillary calcifications on sonography and conventional tomography had a sensitivity of 72% and a specificity of 97%. The sensitivity and specificity of non-specific signs such as hypertension, anaemia, sterile pyuria, bacteriuria and proteinuria were insufficient to be helpful in diagnosis of analgesic nephropathy in patients with end-stage renal disease. The results of this study were corroborated by the second study, conducted in 12 European countries and Brazil.

The third study compared the usefulness of sonography, conventional tomography, and computerized tomography (CT) without contrast medium for the diagnosis of analgesic nephropathy (Fig. 27.1). In the 40 patients with end-stage renal disease, renal size could be evaluated with similar accuracy with all three techniques, but CT scanning was the best method for detecting papillary calcifications (sensitivity, 87%; specificity, 97%) (Table 27.1). The results were similar for the group of 53 patients with incipient, mild or moderate renal failure (serum creatinine concentration, 1.5–4 mg/dl (133–354 μmol/l). The sensitivity of CT scanning for papillary calcifications was 92% with a specificity of 100% (Table 27.1). The finding of papillary calcifications in the early stages of analgesic nephropathy corroborates experimental observations in rats.

On the basis of the results of these studies, CT scanning without contrast medium is recommended to diagnose or rule out analgesic nephropathy as the possible cause of renal disease in patients with end-stage renal disease as well as those with mild and moderate renal failure, even in the absence of reliable information on the use of analgesics.

**Risk factors for analgesic nephropathy**

In nearly all initial reports of analgesic nephropathy, the patients had taken large amounts of products containing phenacetin, which led to the hypothesis that phenacetin was the nephrotoxic culprit. Consequently, phenacetin was removed from analgesic mixtures.
Fig. 27.1 Diagnostic criteria of analgesic nephropathy (AN). (a) Macroscopic aspect of an AN kidney from a patient with ESRD. (b) Diagnostic criteria used. (c) CT scans without contrast material of an individual with normal kidneys and patients with AN and with stage 3 CKD and ESRD.²

Table 27.1 Sensitivity and specificity of CT imaging criteria used to diagnose analgesic nephropathy in 40 patients with end-stage renal disease (ESRD) and 53 patients with incipient, mild or moderate renal failure (RF)*

<table>
<thead>
<tr>
<th>Finding on renal imaging</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<tr>
<td>Decrease in length</td>
<td></td>
<td></td>
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<tr>
<td>patients with ESRF</td>
<td>95</td>
<td>10</td>
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<tr>
<td>patients with RF</td>
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<td>86</td>
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<td>Bumpy contours</td>
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<td>patients with ESRF</td>
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<td>90</td>
</tr>
<tr>
<td>patients with RF</td>
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<td>93</td>
</tr>
<tr>
<td>Papillary calcifications</td>
<td></td>
<td></td>
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<tr>
<td>patients with ESRF</td>
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<td>97</td>
</tr>
<tr>
<td>patients with RF</td>
<td>92</td>
<td>100</td>
</tr>
<tr>
<td>Decrease in length and either bumpy contours or papillary calcifications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>patients with ESRF</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>patients with RF</td>
<td>77</td>
<td>100</td>
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</tbody>
</table>

* CT was performed without contrast medium. In patients with incipient, mild or moderate renal failure, serum creatinine concentration ranged from 1.5 to 4 mg/dl (133–354 mol/l).
in some European countries, the USA and Australia. After reviewing the data, Prescott challenged this view, because in experimental conditions the nephrotoxic potential of the other analgesics invariably taken with phenacetin is similar to that of phenacetin and may even be greater.

This epidemiological evidence concerning the types of analgesics (single agents versus mixtures) and the different substances causing analgesic nephropathy is limited and controversial as all the studies suffer from one or more methodological weakness(es). Clinical observations pointed to the nephrotoxicity of analgesic mixtures whether or not they contained phenacetin. Two prospective case–control studies (Fig. 27.2) showed a clear association between habitual analgesic consumption and renal functional impairment. Because of the small number of patients with analgesic abuse who had signs of renal impairment, the nephrotoxicity of particular types of analgesic mixtures could not be analyzed. In contrast, the case–control design of several other studies did allow such an analysis (Fig. 27.2). For analgesic mixtures, particularly those containing phenacetin and acetaminophen, nephrotoxicity was demonstrated. No consistent results were obtained with respect to single analgesics.

Additional evidence of the nephrotoxicity of various analgesic mixtures came from a cohort of 226 patients with documented abuse of analgesics and a clear diagnosis of analgesic nephropathy. All but seven patients admitted abusing analgesic mixtures containing caffeine, codeine or both. In 46 patients with no previous phenacetin consumption, classic analgesic nephropathy was associated with the following combinations: aspirin and acetaminophen, aspirin and a pyrazolone, acetaminophen and a pyrazolone, and two pyrazolones, all of which were combined with caffeine, codeine or both. The pyrazolones included antipyrine, salipyrine, aminopyrine and dipyrone.

In a recent large-scale case–control study in Germany and Austria, a dose-dependent significantly increased risk of end-stage renal disease was found in high users of combined or single formulations of phenacetin-free analgesics.

Acetaminophen

An important question that remains incompletely resolved is the renal risk of monotherapy with acetaminophen (paracetamol), which is the primary metabolite of phenacetin and which is now widely used as a minor analgesic. Three recent studies suggest that acetaminophen alone is nephrotoxic, although the risk is probably less than that of phenacetin–aspirin combinations. This difference in risk could be due to acetaminophen having less intrinsic nephrotoxicity than phenacetin. Alternatively, if acetaminophen and phenacetin had the same risk when used in combination with other analgesics, but less risk when used alone, case–control studies would show a lower risk for acetaminophen relative to phenacetin. This would occur because acetaminophen is used both alone and in combinations, whereas phenacetin was always used in combinations, never as a single agent. This hypothesis is supported by one study showing that the risk of acetaminophen and phenacetin combinations was similar.

That acetaminophen alone is nephrotoxic is described in one case–control study of patients with end-stage renal failure. There were, however, important methodological problems with this study. In particular, it could not be excluded that patients with
**ACETAMINOPHEN** 375

Fig. 27.2 Overview of epidemiological studies investigating the renal risk of analgesic consumption. (a) Description of methodological details used in the included studies. (b) Consumption of ‘any analgesic’ exceeding the mentioned dosage. (c) Presentation of OR with 95% CI published in the included epidemiological studies focusing separately on the ingredients: Aspirin, paracetamol and NSAIDs.²
renal disease were more likely to have symptoms requiring analgesics and confounding by indication may have occurred whereby patients with renal disease are taking acetaminophen because they were told to avoid aspirin and NSAIDs.

The latter issues may have been less important in another study that looked at analgesic use in 554 adults presenting with new renal insufficiency (plasma creatinine concentration ≥1.5 mg/dl (13 μmol/l)), rather than end-stage renal disease. This study estimated that the adjusted odds ratio for renal disease was 3.21 in patients taking daily acetaminophen. There was no increase in risk with weekly or less frequent use. The greater frequency with which acetaminophen is taken alone rather than in combination with aspirin may explain the apparently greater risk seen with phenacetin.

In summary, the withdrawal of phenacetin from the market did not completely eradicate analgesic nephropathy. There is experimental, pharmacological and epidemiological evidence that other analgesic mixtures that do not contain phenacetin can also become nephrotoxic and may produce the classic renal lesions of the disease. There is suggestive but not definitive evidence that chronic, especially daily acetaminophen use may have dose-dependent long-term nephrotoxicity.

Chronic renal failure and analgesic use

A small number of epidemiological studies generated the hypothesis that habitual analgesic use influences the progression of chronic renal disease. Given the study designs, however, it is impossible to determine whether exposure to analgesics is the initial cause of renal failure or a factor contributing to the progression of the renal disease, whether there is an interplay between the two possibilities, or whether the association is non-causal. Furthermore, the only clearly increased odds ratios for chronic renal failure were found in the groups of patients with interstitial nephritis and end-stage renal disease from unclear causes, a finding that corroborates the well-documented clinicopathological entity of classic analgesic nephropathy.

The association between chronic renal failure from any cause and excess analgesic use reported by these three case–control studies does not establish cause and effect. In any analysis of these studies, flaws in the study design, inaccurate renal diagnoses and confounding by indication (protopathic bias) have to be considered. Further investigation is needed to determine whether habitual analgesic use influences the progression of chronic renal disease.

Although the collective evidence suggests that habitual analgesic use may be associated with the development of chronic renal failure, it does not conclusively establish a causal link between use/abuse of specific analgesics, particularly acetaminophen, and chronic renal failure. Whether habitual analgesic use influences the progression of chronic renal disease also needs more solid scientific data. Improvements in study design could include the following:

- patients with early stage disease should be included, avoiding the possibility that renal disease provoked analgesic use/abuse (indication, protopathic bias)
- explicit knowledge of both the time in which the drug was started and stopped, and the amount and composition of drug ingested should be obtained (information, ingredient bias)
personal, not telephone, interviews should be performed, and must include visual (book with colour photographs) aids to obtain accurate information concerning the type of drug ingested

- patients and control individuals should be drawn from the same population source, and should be of adequate number to determine statistical significance (detection bias).

The study that realized the best possible approach to evaluate a possible effect of analgesics on the progression of chronic kidney disease is that of Mackinnon et al.\textsuperscript{23}

The authors studied patients with chronic kidney disease of undetermined cause associated with important use of analgesics in which the stoppage or ongoing analgesic use was registered regularly along with several measurements of renal function of a median follow-up period of 58 months. Patients were considered to have analgesic nephropathy when they had a history of analgesic ingestion on a daily basis (excluding low-dosage aspirin as an anti-platelet agent) for at least 3 years and no other explanation for their renal impairment could be found. NSAIDs, analgesic mixtures and paracetamol, all or not in combination, were used. No patient gave a history of phenacetin ingestion. During follow-up, 27 patients were judged to have ceased all analgesic intake, whereas the remaining 51 continued using one or more of the preparations listed.

There were no significant differences between the two groups in terms of racial background, gender, age or proteinuria at presentation. The proportion of patients in each group with a history of smoking, hypertension or vascular disease was not significantly different, either. Despite these similarities, the renal function of those who continued to take analgesics declined 3.5 ml/min/year faster than the patients who stopped taking all analgesics. In addition, continuing analgesics conferred a sixfold increase in the risk for death or progression to ESRD. Despite some flaws in this study, it supports the contention that the continued use of non-phenacetin-combined or single-agent analgesics is associated with faster progression of renal impairment and an increased risk for reaching a combined end-point of death or ESRD in patients with analgesic nephropathy.

Pathogenesis

The nephrotoxicity of analgesics is dose-dependent.\textsuperscript{2,20} Decreased concentrating ability or a mild reduction in glomerular function rate can be seen after cumulative phenacetin, part of analgesic mixtures, intake of as little as 1 kg. In comparison, clinically evident renal disease requires a minimum intake of 2–3 kg each of phenacetin and aspirin. This will take 6–8 years in a patient ingesting six to eight tablets (or about 1 g) of phenacetin-containing compounds per day.

The renal damage induced by analgesics is most prominent in the medulla. The earliest changes consist of prominent thickening of the vasa recta capillaries (capillary sclerosis) and patchy areas of tubular necrosis; similar vascular lesions can be found in the renal pelvis and ureter, suggesting that the primary effect is damage to the vascular endothelial cells.\textsuperscript{24} Later changes include areas of papillary necrosis and secondary cortical injury with focal and segmental glomerulosclerosis and interstitial infiltration and fibrosis.

The mechanisms responsible for the renal injury are incompletely understood. Phenacetin is metabolized to acetaminophen and the reactive intermediates that can injure cells, in part by lipid peroxidation.\textsuperscript{25} These metabolites tend to accumulate in
the medulla along the medullary osmotic gradient (created by the countercurrent system). As a result, the highest concentrations are seen at the papillary tip, the site of the initial vascular lesions. The potentiating effect of aspirin with both phenacetin and acetaminophen may be related to two factors. First, acetaminophen undergoes oxidative metabolism by prostaglandin H synthase to reactive quinoneimine that is conjugated to glutathione. If acetaminophen is present alone, there is sufficient glutathione generated in the papillae to detoxify the reactive intermediate. If the acetaminophen is ingested with aspirin, the aspirin is converted to salicylate and salicylate becomes highly concentrated in both the cortex and papillae of the kidney. Salicylate is a potent depletor of glutathione. With the cellular glutathione depleted, the reactive metabolite of acetaminophen then produces lipid peroxides and arylation of tissue proteins, ultimately resulting in necrosis of the papillae (Fig. 27.3). Second, aspirin inhibits prostaglandin production by inhibition of cyclooxygenase enzymes. Renal blood flow is very dependent on systemic as well as local production of vasodilatory prostaglandins.

**Fig. 27.3** Acetaminophen (paracetamol) active metabolism by prostaglandin H synthase to reactive quinoneimine that is conjugated to glutathione. If acetaminophen is present alone, there is sufficient glutathione generated in the papillae to detoxify the reactive intermediate. If the acetaminophen is ingested with aspirin, the aspirin is converted to salicylate and salicylate becomes highly concentrated in both the cortex and papillae of the kidney. Salicylate is a potent depletor of glutathione. With the cellular glutathione depleted, the reactive metabolite of acetaminophen then produces lipid peroxides and arylation of tissue proteins, ultimately resulting in necrosis of the papillae. Adapted from and.
This is especially true for renal medulla, which normally lives at the edge of hypoxia and therefore is more prone to ischaemic damage.

**Course and complications**

The course of the renal disease depends both on the severity of the renal damage at the time of presentation and upon whether drug therapy is discontinued.\(^4,29,30\) The decline in renal function can be expected to progress if analgesics are continued. Even aspirin, which is generally not nephrotoxic when given alone,\(^14\) could promote further renal damage in analgesic nephropathy.\(^29,30\)

On the other hand, renal function stabilizes or mildly improves in most patients if analgesic consumption is discontinued.\(^29,30\) If, however, the renal disease is already advanced, then progression may occur in the absence of drug intake, presumably due to secondary haemodynamic and metabolic changes associated with nephron loss.\(^30\)

The late course of analgesic nephropathy also may be complicated by two additional problems: malignancy and atherosclerotic disease.

Transitional cell carcinomas of the renal pelvis, ureter and bladder (which maybe multiple and bilateral) all occur with increased frequency in this setting.\(^31–33\) The incidence of renal cell carcinoma also may be enhanced, but this remains controversial.\(^34\)

It is estimated that a urinary tract malignancy will develop in as many as 8–10% of patients with analgesic nephropathy,\(^31–33\) but in well under 1% of phenacetin-containing analgesic users without kidney disease.\(^35\) In women under the age of 50, for example, analgesic abuse is the most common cause of bladder cancer, an otherwise unusual disorder in young women.\(^33\) The potential magnitude of this problem has also been illustrated by histological examination of nephrectomy specimens obtained prior to renal transplantation; the incidence of urothelial atypia in this setting approaches 50%.\(^31\)

The tumours generally become apparent after 15–25 years of analgesic abuse,\(^31\) usually but not always in patients with clinically evident analgesic nephropathy.\(^32\) Most patients are still taking the drug at the time of diagnosis, but clinically evident disease can first become apparent several years after cessation of analgesic intake and even after renal transplantation has been performed.\(^31\) In Australia, for example, the incidence of analgesic nephropathy declined progressively in the first 10 years after phenacetin-containing compounds were removed from over-the-counter analgesic combinations and 5 years after over-the-counter sales of analgesic mixtures were banned.\(^36\) In comparison, the incidence of urinary tract malignancy continued to rise (at a greater rate than other malignancies), a possible reflection of late phenacetin-induced injury.\(^37\)

It is presumed that the induction of malignancy results from the intrarenal accumulation of N-hydroxylated phenacetin metabolites that have potent alkylating action.\(^32\) Because of urinary concentration, the highest concentration of these metabolites will be in the renal medulla, ureters, and bladder, possibly explaining the predisposition to carcinogenesis at these sites. The pathogenetic importance of phenacetin metabolites is suggested indirectly from the observation that there appears to be no association with tumour formation with the prolonged ingestion of other analgesics that can cause papillary necrosis but do not form these metabolites, such as acetaminophen and the NSAIDs.\(^37–39\) The major presenting symptom of urinary tract malignancy in analgesic nephropathy is microscopic or gross haematuria. Thus, continued monitoring...
is essential, and new haematuria should be evaluated with urinary cytology, and, if indicated, cystoscopy with retrograde pyelography. It may also be prudent to obtain yearly urine cytology for the first several years if analgesics are discontinued or indefinitely if drug intake persists. The incidence of urothelial carcinoma after renal transplantation in patients with analgesic nephropathy is comparable to the general incidence of up to 10% of urothelial carcinomas in end-stage renal failure patients with analgesic nephropathy. Removal of the native kidneys prior to renal transplantation has also been suggested, but the efficacy of this regimen has not been proven.

Table 27.2 Analgesics and the kidney

<table>
<thead>
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<th>Is analgesic nephropathy an identifiable disease entity?</th>
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<tr>
<td>Analgesic nephropathy is a chronic renal disease characterized by renal papillary necrosis and chronic interstitial nephritis caused by prolonged and excessive consumption of analgesic mixtures. Analgesic nephropathy is easily diagnosed by a CT scan with contrast material, demonstrating bumpy contours of small kidneys presenting papillary necrosis.</td>
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</table>

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<tr>
<th>What kind of analgesics are associated with analgesic nephropathy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is invariably caused by compound analgesic mixtures containing aspirin or antipyrine in combination with phenacetin, paracetamol or salicylamide, and caffeine or codeine in popular 'over-the-counter' proprietary mixtures.</td>
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</tbody>
</table>

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<th>Is there a risk of chronic renal failure associated to the regular use of single analgesics?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin: no evidence</td>
</tr>
<tr>
<td>Paracetamol: no clear evidence; almost all studies suffer from 'ingredient bias'</td>
</tr>
<tr>
<td>NSAIDs:</td>
</tr>
<tr>
<td>(a) acute renal failure: clear evidence;</td>
</tr>
<tr>
<td>(b) chronic renal failure: no evidence;</td>
</tr>
<tr>
<td>(c) acute on chronic: positive risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Does regular analgesic use contribute to the progression of renal diseases?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive evidence. However, it is impossible to rule out bias caused by the consumption of these analgesics for symptoms of the conditions that predisposed patients to renal failure.</td>
</tr>
</tbody>
</table>

Analgesic nephropathy is a form of renal disease characterized by renal papillary necrosis and chronic interstitial nephritis caused by prolonged and excessive consumption of analgesic mixtures.

It is invariably caused by compound analgesic mixtures containing aspirin or antipyrine in combination with phenacetin, paracetamol, or salicylamide and caffeine or codeine in popular 'over-the-counter' proprietary mixtures.*

Acetaminophen undergoes oxidative metabolism by prostaglandin H synthase to reactive quinoneime that is conjugated to glutathione. If acetaminophen is present alone, there is sufficient glutathione generated in the papillae to detoxify the reactive intermediate. If the acetaminophen is ingested with aspirin, the aspirin is converted to salicylate and salicytate becomes highly concentrated in both the cortex and papillae of the kidney. Salicylate is a potent depletor of glutathione. With the cellular glutathione depleted, the reactive metabolite of acetaminophen then produces lipid peroxides and arylation of tissue proteins, ultimately resulting in necrosis of the papillae.
Patients with analgesic nephropathy are more likely to develop premature ageing and greying and atherosclerotic vascular disease (including myocardial infarction and thrombotic stroke). As examples, chronic ingestion of phenacetin-containing analgesic mixtures in women aged 30–49 is, after 20 years, associated with a twofold increase in risk of myocardial infarction and a threefold increase in risk of all cardiovascular diseases. It is possible that the analgesic microangiopathy that is the earliest sign of renal injury may play an important role in this problem; the incidence of other risk factors (such as hypercholesterolemia, smoking and hypertension) does not appear to be enhanced when compared with patients with other forms of chronic renal failure.

**Take home points** (Table 27.2)

1. Classic analgesic nephropathy is a specific renal disease characterized by renal papillary necrosis and chronic interstitial nephritis caused by prolonged and excessive consumption of analgesic mixtures.

2. Analgesic nephropathy can be accurately diagnosed at any stage by CT scanning without contrast medium, even in the absence of reliable information on previous analgesic use.

3. The effects of habitual use of analgesics alone or in combination on the progression of other forms of renal disease remain unclear.

4. Well-designed studies are needed to define the nephrotoxicity of analgesics in patients with renal disease. In the meantime it is prudent to continue to advise these patients that acetaminophen should be the non-narcotic analgesic of choice for intermittent use.

**References**

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest


   **Summary of current evidence on analgesic nephropathy.**


Study identifying the good performance of the CT scan in the diagnosis of AN even in the absence of any drug history of the patient.


Excellent overview and critical analysis of the literature of that time


REFERENCES

Many conventional anti-rheumatic medications are nephrotoxic; some therapies are contraindicated in patients with renal impairment whereas others are allowed after dose reduction. In addition, several drugs can induce renal impairment in previously normal kidneys. Previously, treatment of patients’ rheumatic disease in the presence of renal impairment was often compromised. However, new biological therapies have so far been associated with low renal toxicity and this has opened up new therapeutic avenues.

In this chapter, the renal side effects of common anti-rheumatic medications will be outlined along with implications for patients with renal impairment. Guidance regarding routine monitoring will be given (Table 28.1).

**Methotrexate**

Methotrexate (MTX) is used commonly as first-line therapy for rheumatoid arthritis (RA) both alone and in combination with sulfasalazine (SSA) and/or hydroxychloroquine (HC). It is also used in the treatment of spondyloarthropathies, connective tissue diseases such as systemic lupus erythematosus (SLE) and vasculitides including Wegener’s granulomatosis. Many of the new biological therapies have been shown to be more efficacious in the treatment of RA when used in combination with MTX, so co-administration is common.

MTX reduces purine biosynthesis via inhibition of the enzyme dihydrofolate reductase (DHFR) and other folate-dependant enzymes. Via inhibition of the enzyme 5-aminomimidazole-carboxamide-ribinucleotide-transformylase, MTX increases adenosine release leading to inhibition of neutrophil chemotaxis and other anti-inflammatory effects. MTX and its metabolites are mainly eliminated via the kidney, hence the dose of MTX must be reduced in renal impairment and its use is contraindicated in the presence of significant renal disease. Calculation of creatinine clearance in patients with renal impairment and at-risk groups such as the elderly can guide dosage reduction. It is probable that all non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, decrease MTX clearance. Using microdialysis techniques in rats, time–concentration area under the curves for MTX and its major metabolite, 7-hydroxymethotrexate (7-OH-MTX) have been shown to increase about twofold in the presence of naproxen. Although clinical effects are uncommon with low-dose MTX, the effect may be significant.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Use in renal impairment</th>
<th>Renal toxicity</th>
<th>Monitoring for renal toxicity*</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Methotrexate | Reduce dose in renal impairment  
Contraindicated in severe renal disease | Uncommon: renal insufficiency, nephropathy  
Very rare: dysuria, cystitis, haematuria | Renal function prior to therapy  
Renal function every 2 weeks until dose and monitoring stable for 6 weeks; thereafter monthly, until the dose and disease is stable for a year. Thereafter consider reducing frequency of monitoring to every 2–3 months | Interaction with NSAIDs |
| Sulfasalazine | Caution | Common: proteinuria  
Reported: nephrotic syndrome, interstitial nephritis, crystalluria, haematuria | Renal function and urinalysis prior to therapy | Adequate fluid intake to reduce crystalluria |
| Hydroxychloroquine | Caution | None | Renal function prior to therapy | More frequent eye monitoring if renal insufficiency |
| Cyclosporine and FK-506 | Contraindicated in patients with abnormal renal function | Very common: hypertension, acute and chronic renal impairment  
Common: hyperkalaemia, (especially in patients with renal dysfunction) | Prior to therapy: renal function twice, 2 weeks apart to obtain mean. Creatinine clearance or equivalent. BP: ≤140/90 on two occasions at 2/52 apart  
On therapy: renal function (inc. potassium) every 2 weeks until dose and results stable for 3 months and then monthly  
BP each visit | Renal impairment during the first few weeks is generally dose-dependent and usually responds to dose reduction. Structural changes in the kidney may occur long term  
Interaction with NSAIDs (especially diclofenac) requires closer monitoring  
Caution required when co-administered with potassium-sparing drugs |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leflunomide</strong></td>
<td>Contraindicated in moderate to severe renal insufficiency and in severe hypoproteinaemia</td>
<td>Common: mild hypertension&lt;br&gt;Rare: severe hypertension&lt;br&gt;Reported: renal failure</td>
<td>Renal function prior to therapy&lt;br&gt;Blood pressure each visit</td>
</tr>
<tr>
<td><strong>Azathioprine</strong></td>
<td>Reduce dose in renal insufficiency</td>
<td>Reported: interstitial nephritis and multi-organ failure</td>
<td>Renal function prior to therapy then 6-monthly</td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>Caution in patients with renal impairment</td>
<td>Reported: haemorrhagic cystitis, bladder cancer</td>
<td>Urinalysis during therapy and monitor long term if haemorrhagic cystitis occurs&lt;br&gt;Use mesna to reduce urotoxic effect with high-dose regimes</td>
</tr>
<tr>
<td><strong>Mycophenolate</strong></td>
<td>Caution in renal impairment</td>
<td>Reported: renal impairment</td>
<td>Renal function prior to therapy&lt;br&gt;No renal monitoring required</td>
</tr>
<tr>
<td><strong>Myocrisin injection</strong></td>
<td>Caution in mild renal impairment&lt;br&gt;Contraindicated in severe renal disease</td>
<td>Proteinuria, nephritic, haematuria</td>
<td>Renal function and urinalysis prior to therapy&lt;br&gt;Urinalysis prior to each injection&lt;br&gt;Presence of albuminuria may indicate developing toxicity&lt;br&gt;Caution with concomitant use of renal-toxic drugs</td>
</tr>
<tr>
<td><strong>Penicillamine</strong></td>
<td>Contraindicated in moderate to severe renal impairment</td>
<td>Proteinuria up to 30%&lt;br&gt;Reported: nephrotic syndrome, glomerulonephritis, Goodpasture's syndrome</td>
<td>Renal function and urinalysis prior to therapy&lt;br&gt;Urinalysis every 2 weeks until dose and monitoring stable for 3 months; monthly thereafter&lt;br&gt;Caution with concomitant use of renal-toxic drugs especially NSAIDs</td>
</tr>
<tr>
<td><strong>Chlorambucil</strong></td>
<td>Myelosuppression more likely if renal impairment</td>
<td>Very rare: sterile cystitis</td>
<td>None</td>
</tr>
<tr>
<td><strong>Infliximab</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Etanercept</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Adalimumab</strong></td>
<td>Not studied</td>
<td>Reported: renal impairment</td>
<td>None</td>
</tr>
</tbody>
</table>

(Continued)
Table 28.1 (continued) Renal side effects of anti-rheumatic medication and biologicals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use in renal impairment</th>
<th>Renal toxicity</th>
<th>Monitoring for renal toxicity*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certolizumab</td>
<td>Not studied</td>
<td>Reported: renal impairment</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>No dose adjustment in patients with mild renal impairment. Has not been studied in moderate to severe renal impairment</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Anakinra</td>
<td>Caution in renal impairment</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>Not studied</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>Not studied</td>
<td>None reported in clinical trials</td>
<td>Not licensed</td>
<td></td>
</tr>
<tr>
<td>Abatacept</td>
<td>Not studied</td>
<td>None reported in clinical trials</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

*BSR Monitoring Guidelines 2009 [does not include recommendations for biologic therapies]

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000).

Reported: incidence cannot be estimated from the available data.

BP, blood pressure; NSAIDs, non-steroidal anti-inflammatory drugs.
in patients receiving higher weekly maintenance doses. In addition, combination therapy with MTX and aspirin has been shown to be associated with deterioration in renal function as measured by plasma clearance of radiolabelled ethylenediaminetetraacetic acid (EDTA) and mercaptoacetyltiglyceride.

The most common major side effects of MTX therapy are marrow suppression, hepatotoxicity and pneumonitis. Renal toxicity is rare but the risk is increased in patients with pre-existing renal impairment and reduced renal clearance.

SSA

SSA is used frequently in inflammatory arthritis. The mechanism of action is not clear, but the number of activated lymphocytes is reduced and the titres of immunoglobulin (Ig)M and rheumatoid factor both fall. The active component, sulfapyridine is liberated from SSA in the colon and following absorption, is metabolized by N-acetylation, ring hydroxylation and subsequent glucuronation. Individual differences in the rate of acetylation and oxidation leads to variations in steady state plasma concentrations of sulfapyridine. There is some evidence for an association between acetylator gene haplotypes and the incidence of non-renal toxicity particularly in Japanese patients.

Serious side effects are most common in the first 12 weeks of therapy and include leucopaenia and hepatotoxicity. Patients should be warned to expect orange discoloration of the urine. Although serious renal side effects are rare, a few cases of SSA-induced renal failure have been reported and the manufacturer recommends renal function monitoring although without scientific logic. SSA has also been reported to cause proteinuria and nephrotic syndrome and regular testing for proteinuria should be ensured during treatment as SSA can cause crystalluria and kidney stone formation. Adequate fluid intake should be ensured during treatment as SSA can cause crystalluria and kidney stone formation.

Anti-malarials

Hydroxychloroquine is used to treat RA and SLE. The dominant mechanism of action is unclear, but accumulation in lysosomes of leucocytes and fibroblasts may interfere with antigen processing. In addition, interleukin-1 production by macrophages and monocytes is reduced. Apart from the rare cumulative side effect of retinopathy, the majority of adverse events are transient and not serious. Anti-malarials are not reported to cause any renal toxicity, but increased monitoring for retinal toxicity is recommended in the presence of renal impairment.

Calcineurin inhibitors

Cyclosporine A (CsA) and tacrolimus (FK-506) are calcineurin inhibitors (CI) used in the treatment of rheumatological diseases. CsA is licensed for use in RA and is also used in the treatment of psoriatic arthritis and connective tissue diseases. FK-506 is used for refractory severe connective tissue diseases.

CsA and FK-506 bind cyclophilin and FK-binding protein (FKBP), respectively, and the resulting complex inhibits calcineurin, a calcium calmodulin-dependent phosphatase with normal function to dephosphorylate a nuclear regulatory protein (nuclear factor
of activated T cells (NF-AT)). Translocation of NF-AT to the nucleus is prevented and transcription of T cell activating genes (interleukin (IL-2, IL-3, IL-4 and interferon γ) is inhibited. CsA also up-regulates transforming growth factor-β (TGF-β), which decreases T-cell activation. CI can also directly inhibit B cell and polymorphonuclear leucocyte function.

CsA and FK-506 are associated with significant renal toxicity including hypertension, acute renal dysfunction and chronic nephropathy. Hypertension is common, due to multiple mechanisms and is usually dose-dependent. Acute impairment of renal function occurs early in therapy and is probably secondary to afferent arteriolar vasoconstriction, which reduces glomerular filtration rate inducing a rise in serum creatinine. This is dose-dependent and responds to a dose reduction. Chronic renal dysfunction is associated with long-term therapy of 6–12 months and in some cases the serum creatinine does not rise. The risk increases with length of exposure and cumulative dose; a dose of >5 mg/kg increases the risk. Chronic renal dysfunction can occur at lower doses in the elderly, patients with previous episodes of acute renal toxicity on a CI, pre-existing renal dysfunction and co-administration with other nephrotoxic drugs or drugs that inhibit P450 3A4 (increase CI levels) such as calcium channel blockers, anti-fungal agents and erythromycin. Characteristic histological features include interstitial fibrosis, tubular atrophy and glomerular sclerosis. These changes are often irreversible and not responsive to dose reduction/drug cessation. The changes may lead to progressive renal failure and end-stage renal disease.

**Leflunomide**

Leflunomide is used in the treatment of RA and spondyloarthopathies such as psoriatic arthritis. It is licensed as monotherapy, but is often used in combination with MTX in refractory cases. An active metabolite inhibits the enzyme dihyoorotate dehydrogenase, which is involved in de novo pyrimidine synthesis that is especially required by activated lymphocytes. The active metabolite is further metabolized and then renally excreted. Leflunomide is contraindicated in patients with moderate to severe renal insufficiency and in severe hypoproteinaemia, e.g. nephrotic syndrome.

Leflunomide can induce a global rise in blood pressure, especially in patients with pre-existing hypertension.

**Azathioprine**

Azathioprine (AZA) is used in the treatment of rheumatoid arthritis, systemic lupus and vasculitis. AZA interferes with adenine and guanine ribonucleotides via suppression of inosinic acid synthesis. AZA is cleaved to 6-mercaptopurine (6-MP), which is metabolized inside cells to thioinosinic and thioguanylic acid through the action of hypoxanthine phosphororrisyltransferase (HGPRT). These secondary intracellular metabolites are responsible for the effect of AZA, making measurement of blood or plasma levels of AZA unlikely to be very useful. Xanthine oxidase is also involved in AZA metabolism and is inhibited by allopurinol leading to accumulation and increased toxicity of AZA and metabolites. There are two distinct populations of AZA metabolizers: fast
and slow, leading to a fourfold variation in the rate of clearance. In addition, the enzyme that metabolizes 6-MP (thiopurine methyltransferase (TPMT)) exhibits genetic polymorphism with a small subset of the population producing low levels. This leads to increased toxicity (usually bone marrow suppression) on low doses of AZA in these patients. Although of unproven clinical value, TPMT activity testing prior to commencing therapy is becoming increasingly common.

The principle toxicities of AZA include marrow suppression and gastrointestinal upset. The dose of AZA should be reduced in severe renal impairment.\(^1\),\(^2\) AZA can rarely induce a hypersensitivity reaction, which in severe cases manifests as multiple organ failure.\(^13\) Patients present with fever, hypotension and oliguria a few days after commencing AZA or increasing the dose. The reaction may be due to cytokine or mediator release induced by AZA. A case has been reported of a patient who developed end-stage renal failure following AZA hypersensitivity mimicking Goodpasture’s syndrome.\(^14\) In a separate case report, a patient developed fever, hepatitis and acute interstitial nephritis after 3 weeks of AZA therapy, which recurred on recommencing the drug.\(^15\)

**Cyclophosphamide**

Cyclophosphamide (CTX) pulse therapy (usually intravenous) is commonly used for the management of severe SLE, systemic sclerosis and vasculitis. Continuous oral CTX is rarely used in rheumatology patients as it is generally thought that this method of administration is associated with a greater incidence of toxicity.\(^16\) Active metabolites of CTX produced in the liver prevent lymphocyte replication via DNA cross-linking. The kidney excretes CTX and metabolites, therefore the dose of CTX must be reduced if renal impairment is present.\(^1\),\(^2\) Allopurinol and cimetidine inhibit hepatic microsomal enzymes, resulting in increased CTX toxicity. The most common toxic effects include gastrointestinal upset, increased risk of malignancy, infertility, cumulative bone marrow toxicity and haemorrhagic cystitis.\(^1\),\(^2\) The urological toxicity of CTX is due to its metabolite acrolein, which is excreted in the urine. If high doses of intravenous CTX are used, the risk of haemorrhagic cystitis can be reduced by co-administration of mesna with each pulse and assuring adequate patient hydration. The development of non-glomerular haematuria during CTX therapy is associated with an increased risk of subsequent bladder malignancy\(^17\) and these patients should be followed long term. Rarely renal cell carcinoma may develop following CTX therapy\(^18\) and therefore cytology should be included with screening.

**Mycophenolate mofetil**

Mycophenolate is used in patients with severe SLE and vasculitis. Mycophenolate is metabolized to the active metabolite mycophenolic acid. The mechanism of action is via inhibition of the enzyme inosine monophosphate dehydrogenase (IMPDH), which leads to inhibition of cellular and humoral immunity. The major toxicity is marrow suppression and gastrointestinal upset.\(^1\),\(^2\) Mycophenolate has been shown to be effective in the treatment of renal complications of SLE.\(^19\)
Gold therapy

Injectable gold (sodium aurothiomalate) has gone from standard of care to being used only occasionally in the treatment of patients with RA. Aurothiomalate has been found to inhibit the binding of transcription factors to DNA and hence may regulate gene expression. Toxicity can be divided into two groups. \(^1\,^2\) Mucocutaneous reactions and anorexia tend to occur early during therapy and are likely to be a direct toxic effect of the drug. The second group consists of reactions that may involve an immunological mechanism and include renal toxicity, blood dyscrasias and hypersensitivity pneumonitis.

Gold therapy should be avoided in renal impairment and is contraindicated in severe renal disease. \(^1\,^2\) Transient and minor proteinuria occurs commonly (10%) and urine should be tested with each injection. \(^11\) Minor proteinuria usually responds to suspension of gold therapy and exclusion of urinary tract infection. Gold therapy should be discontinued in the presence of persistent proteinuria at greater than 300 mg/l. Deterioration of renal function due to gold is unusual. Rarely, nephrotic syndrome develops, which always resolves, but may take months or years. \(^20\) Occasionally, membranous glomerulonephritis (GN) associated with immune complex deposition occurs with more severe proteinuria and haematuria. Epimembranous spikes and a mild increase in mesangial cells are unusually seen, and the diagnosis can be confirmed with immunofluorescence/immunoperoxidase microscopy, which shows granular subepithelial deposits of predominately IgG. On electron microscopy, electron-dense deposits are seen. Mesangial GN is found in patients with RA irrespective of therapy, but in patients receiving gold therapy there is an increased association between this histological appearance and haematuria. Immunofluorescence may reveal either granular deposits of immunoglobulin (predominately IgG) and complement, or may be negative. Patients with proteinuria and haematuria following gold therapy have been found to have thinner glomerular basement membranes when compared with controls. \(^21\) Gold may induce a disease of immune-complex type in which circulating immune complexes are either deposited in glomeruli or formed \textit{in situ}. Tubular proteinuria and abnormal tubular function have also been described with gold therapy \(^22\) and gold deposits have been demonstrated in proximal tubular cells. \(^23\) In those patients without renal abnormalities before treatment, renal biopsy should be confined to those who have deteriorating renal function, or who fail to improve after withdrawal of drug. Rechallenge with further gold therapy usually results in repeated toxicity. This may in part be due to an association between renal toxicity and the human leucocyte antigen (HLA) alleles DR3/B8. Poor sulphoxidation ability has been shown to be a risk factor for increased toxicity with gold therapy, although the mechanism is unknown. \(^24\) Shared risk factors may be involved, as patients who develop proteinuria on gold are more likely to do so on penicillamine and vice versa. \(^25\)

D-Penicillamine

D-penicillamine (DPA) is rarely used in the treatment of RA and to treat the skin manifestations of systemic sclerosis. The use in both these conditions is declining, as more efficacious less toxic therapies are now available. The mechanism of action is not
known, but may involve modulation of the immune system via sulphhydryl exchange reactions. In addition, DPA inhibits binding of the transcription factor AP-1 to DNA and therefore may influence gene transcription. DPA is cleared largely through oxidation to form disulphides with plasma albumin, L-cystine, homocysteine and itself. Patients with impaired sulphoxidation status have been shown to have an increased risk of side effects. In addition, increased risk of renal toxicity has been found to be associated with the presence of HLA allele DR3. Although the two risk factors are not additive, the possession of either DR3 or poor sulphoxidation produces a relative risk of toxicity of 25.0. Patients who develop proteinuria with penicillamine are more likely to do so with gold and vice versa.

Toxicity is common (50%), with mucocutaneous reactions, gastrointestinal upset, renal toxicity, blood dyscrasias and autoimmune phenomenon seen. The incidence of side effects with D-penicillamine (DPN) is related to drug dose. Mild proteinuria associated with immune complex nephritis occurs in up to 30% of patients, but may resolve despite continuation of treatment. No significant deterioration in renal function normally occurs. Heavy proteinuria and nephrotic syndrome due to membranous GN should respond to cessation of drug, but may take months or years to resolve. Immunofluorescence reveals granular subepithelial deposits of predominately IgG and on electron microscopy, electron-dense deposits are seen. IgM nephropathy and minimal change nephropathy have also been reported. If haematuria occurs, therapy should be withdrawn immediately as this may indicate rapidly progressive (crescentic) glomerulonephritis due to drug induced Goodpasture’s syndrome or lupus erythematosus or other causes. Goodpasture’s syndrome (with dyspnoea, haemoptysis, pleural effusions, gross haematuria and oliguria) may be associated with the presence of anti-glomerular basement membrane antibodies and haemoptysis and usually requires treatment with high-dose corticosteroids. Occasionally, circulating anti-myeloperoxidase antibodies have been detected in such cases. This rare complication may be fatal in 50% of cases and return of renal function to normal in the survivors is unlikely. DPN has been associated with the anti-DNA (anti-histone) antibodies leading to a syndrome of drug-induced lupus erythematosus. Occasionally, anti-double stranded DNA antibodies are produced, which can induce significant lupus renal disease and proteinuria. DPN has also been implicated in drug-induced acute interstitial nephritis.

Renal biopsy is indicated in patients who develop toxicity on top of pre-existing renal disease or who have declining renal function. Monitoring of patients receiving penicillamine must continue long term, as the renal complications tend to occur several months into treatment.

Chlorambucil

Chlorambucil is used occasionally in patients with rheumatic disease and vasculitis that is resistant to other therapy. Chlorambucil is metabolized to phenylacetic acid mustard, which cross-links DNA inhibiting replication. Chlorambucil and its metabolites are renally excreted and therefore caution is required when prescribing for patients with renal impairment. The most common side effects are cumulative marrow suppression and infertility.
Biological therapy

New anti-rheumatic therapies are now available that can directly target components of the immune response (Table 28.2).

Anti-cytokine therapies

Tumour necrosis factor (TNF)α blockade

Four anti-TNFα therapies are currently licensed and approved for use in inflammatory arthritis (Table 28.2): etanercept, infliximab, adalimumab and certolizumab. These agents are frequently given in combination with MTX to increase efficacy. None of the TNFα blockers have been associated with renal complications and no specific monitoring for renal toxicity is required. The major side effects of these treatments are increased risk of infection, injection site/infusion reactions and potential increased risk of malignancy long term. The most recent data suggest that the risk of malignancy is not higher in the treated group when compared with untreated patients with RA.

IL-6 blockade

Tocilizumab, a humanized IgG1 monoclonal antibody targeted to the IL-6 receptor, has recently been licensed for RA. It is co-administered with MTX in order to increase efficacy. No renal toxicity problems have been reported so far in clinical trials, although its use in patients with severe renal impairment has not been evaluated.

Table 28.2 Biological therapies: Construct and target

<table>
<thead>
<tr>
<th>Drug</th>
<th>Construct</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Chimeric human-murine IgG1 monoclonal antibody</td>
<td>TNFα</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Human TNF receptor p75 Fc fusion protein</td>
<td>TNFα</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Human monoclonal antibody</td>
<td>TNFα</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Humanised antibody Fab fragment conjugated to PEG</td>
<td>TNFα</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Chimeric human-murine IgG1 monoclonal antibody</td>
<td>CD20 (depletes pre-B and mature B lymphocytes)</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>Humanized monoclonal antibody</td>
<td>CD20 (depletes pre-B and mature B lymphocytes)</td>
</tr>
<tr>
<td>Anakinra</td>
<td>IL-1 receptor antagonist</td>
<td>IL-1 receptor</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Humanized IgG1 monoclonal antibody</td>
<td>IL-6</td>
</tr>
<tr>
<td>Abatacept</td>
<td>CTLA-4–IgG1Fc fusion protein</td>
<td>CD80/86 preventing T-cell activation</td>
</tr>
</tbody>
</table>

CTLA, cytotoxic T lymphocyte antigen; Ig, immunoglobulin; IL, interleukin; PEG, polyethylene glycol; TNF, tumour necrosis factor.
IL-1 inhibitor
An IL-1 receptor antagonist (Anakinra) has been licensed for RA, but was found to have low efficacy and its use was not approved by NICE for use in the UK.

B cell therapies
Rituximab, already used extensively in the treatment of B cell lymphomas, has been shown to be efficacious in the treatment of rheumatoid factor-positive RA. Rituximab is a chimeric monoclonal antibody directed against CD20 found on the surface of pre-B cells and mature B lymphocytes. Co-administration of MTX is recommended to reduce the induction of human anti-chimeric antibodies and prevent infusion reactions. Rituximab has also been studied extensively in many other autoimmune diseases including SLE, systemic sclerosis, Sjogren’s syndrome, and Wegner’s granulomatosis and use in these conditions is likely to increase.

No renal toxicity has been reported during the use of rituximab in many thousands of patients with lymphomas or during clinical trials of rituximab in RA.

Ocralizumab is a fully humanized monoclonal antibody also directed against CD20 on pre-B cells and mature B lymphocytes. This therapy is currently undergoing evaluation in RA and other autoimmune diseases.

T cell therapies
Abatacept consists of a fusion protein of cytotoxic T lymphocyte antigen-4 (CTLA-4) and IgG1Fc. Following T cell receptor–MHC/antigen interaction, a second activation signal is provided by the interaction of CD80/CD86 on antigen-presenting cells and CD28 on T cells. Abatacept binds CD80/CD86, blocking this signal and thus interrupts T cell activation.

No significant renal toxicity was seen in clinical trials.

Drugs used for treatment of gout
Colchicine
Colchicine is used for the treatment of acute attacks of gout and for short-term prophylaxis during initiation of therapy with allopurinol in patients who are unable to receive NSAIDs. It also has a prophylactic effect against recurrent attacks. Colchicine interrupts the inflammatory response to tissue deposition of urate crystals via various effects on neutrophils. It can cause renal damage and caution is recommended when prescribing in patients with renal impairment. The dose should be reduced in the presence of renal disease, as it is renally excreted. Administration should be avoided if severe renal disease is present.

Allopurinol
Allopurinol, a xanthine-oxidase inhibitor, reduces the formation of uric acid from purines. It is used for the long-term prevention of attacks. Allopurinol can be used in the presence of renal impairment and urate stones (unlike uricosuric drugs). Allopurinol is
renally excreted so the dose needs to be reduced if renal impairment is present.\(^1\) Rarely, acute interstitial nephritis leading to acute renal failure has been reported.\(^{40}\) In such cases, other features suggesting a hypersensitivity reaction may be present including arthralgia, fever, skin rash and evidence of abnormal liver function and eosinophilia on blood tests. Mild to moderate haematuria and proteinuria are usually present. Treatment includes drug withdrawal and corticosteroids. Allopurinol interacts with azathioprine and cyclophosphamide to increase the toxicity of these drugs.

**Uricosuric drugs**

Probenecid and sulphinpyrazone increase renal excretion of uric acid. These drugs are not effective in the presence of renal impairment and should not be used in the presence of urate stones. Cases of acute renal failure and nephrotic syndrome have been reported.\(^1\)

**Take home points**

1. Many conventional anti-rheumatic medications are nephrotoxic even in previously normal kidneys.
2. Patients must be monitored closely for toxicity while on these medications.
3. New biological medications have so far been associated with low renal toxicity and this has opened up new therapeutic options in patients with pre-existing renal impairment.

**References**

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest


   **The BNF provides UK healthcare professionals with authoritative and practical information on the selection and clinical use of medicines in a clear, concise and accessible manner. Information about all UK licensed medicines can be accessed.**


   **The electronic Medicines Compendium (eMC) contains information about UK licensed medicines. Patient information leaflets (PILs) and Summaries of Product Characteristics (SPCs) can be downloaded.**


**The British Society for Rheumatology is the professional body representing rheumatology doctors in the UK. These guidelines outline standard current practice for monitoring DMARDs.**


Chapter 29

Rheumatological diseases associated with interstitial nephritis

Alan D. Salama and Charles D. Pusey

Introduction

Tubulo-interstitial nephritis (TIN) is an inflammatory renal condition in which the damage is focused on the tubules and interstitium. It is of considerable importance as tubulo-interstitial damage can more closely correlate with impairment of renal function than the degree of glomerular damage. Interstitial inflammation may be secondary to glomerular injury, renovascular or metabolic disease, or may be initiated primarily within the interstitial compartment. The more common causes of TIN are drug reactions, infections and an ‘idiopathic’ group. Many drugs used in rheumatology practice, particularly non-steroidal anti-inflammatory drugs, can lead to TIN; these are considered separately in Chapter 26. A number of systemic diseases are also associated with TIN, many as a result of autoimmune processes, in which tolerance to self-antigens is lost. Those disorders that can induce TIN without glomerular involvement and may be encountered by rheumatologists will form the focus of this chapter (Table 29.1). Most descriptions of these patients are in case reports or small clinical series. As a result, there is a paucity of trial data available regarding treatment options.

Clinical features

TIN may result in acute renal failure, accounting for up to 27% of cases presenting with renal failure and normal sized kidneys. More commonly, however, it may be chronic in nature. Many clinical features are common to TIN irrespective of its aetiology (Table 29.2). However, as suggestive clinical features can be absent or the diagnosis may not be suspected, renal biopsy is required to confirm the diagnosis. It is therefore essential that urine dipstick is routinely performed on patients with systemic disease, so as to alert the physician to ongoing renal inflammation.

Tubular damage occurs consequent to the interstitial inflammation and a number of functional tubular defects may develop, the pattern of which is dependent on the predominant region of the tubule affected (Table 29.3). If widespread interstitial inflammation is present, a mixture of defects may occur. These may result in presenting symptoms, such as renal tubular acidosis leading to hypokalaemic paralysis, or may be subclinical and only evident following specific investigations.
Table 29.1 Associations of tubulo-interstitial nephritis with systemic disease

<table>
<thead>
<tr>
<th>Rheumatological conditions associated with TIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Overlap syndrome/mixed connective tissue disease</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>TINU</td>
</tr>
<tr>
<td>Primary systemic vasculitis</td>
</tr>
<tr>
<td>Relapsing polychondritis</td>
</tr>
</tbody>
</table>

TIN, tubulo-interstitial nephritis; TINU, tubulo-interstitial nephritis and uveitis.

Table 29.2 Presenting features and laboratory findings in TIN

<table>
<thead>
<tr>
<th>Features</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Renal impairment</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td>Rash*</td>
<td>Sterile pyuria</td>
</tr>
<tr>
<td>Flank tenderness</td>
<td>Haematuria</td>
</tr>
<tr>
<td>Gastrointestinal complaints</td>
<td>Proteinuria†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Casts (red cell and granular)</td>
</tr>
<tr>
<td>Oedema</td>
<td></td>
</tr>
<tr>
<td>Oligoanuria</td>
<td></td>
</tr>
</tbody>
</table>

*More common in drug-related cases.
†Generally <1 g/24 hours (adapted from 3).

Table 29.3 Sites of injury and patterns of tubular dysfunction in acute TIN

<table>
<thead>
<tr>
<th>Site of injury</th>
<th>Tubular dysfunction</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubule</td>
<td>Decreased reabsorption of: Na⁺, glucose, HCO⁻³, urate, PO₄⁻³, amino acids</td>
<td>Glycosuria, hypouricaemia, hypophosphataemia, aminoaciduria, alkaline urine, acidaemia*</td>
</tr>
<tr>
<td>Distal tubule</td>
<td>Decreased secretion of: Na⁺, H⁺</td>
<td>Alkaline urine, acidaemia, hyperkalaemia, inability to preserve Na⁺†</td>
</tr>
<tr>
<td>Medulla and papilla</td>
<td>Decreased reabsorption of: Na⁺. Decreased concentrating ability</td>
<td>Polyuria, nocturia, inability to preserve Na⁺‡</td>
</tr>
</tbody>
</table>

*Proximal renal tubular acidosis.
†Distal tubular acidosis.
‡Nephrogenic diabetes insipidus.
Investigations

Ultimately a renal biopsy is required to confirm a diagnosis of TIN, with samples sent for immunohistochemistry, electron microscopy and light microscopy. However, a number of findings suggest the diagnosis in the correct clinical setting.

Serum creatinine may be raised and is often the presenting feature. There may be evidence of systemic acidaemia, hypo- or hyper-kalaemia, hypophosphatemia or hypouricaemia. Fractional excretion of sodium may be raised, but is of use only in patients who have not received diuretics. Peripheral blood eosinophilia may be present, more commonly in cases of allergic aetiology. Immunological tests should be performed in all cases and may be helpful in the diagnosis of systemic disorders associated with TIN. Urine dipstick testing is generally positive for blood and protein, and can also reveal glucose, a low specific gravity and an alkaline pH. Analysis of the urinary sediment reveals both white and red blood cells, with casts of white cells and, less commonly, red cells. Eosinophiluria (>1% of total leucocytes) suggests an allergic aetiology, requires special staining methods, but is neither specific nor sensitive. Urine protein estimation, usually in the form of a spot protein-to-creatinine ratio, or a 24-hour urine collection, shows non-nephrotic range proteinuria. This predominantly consists of low molecular weight proteins, such as β2-microglobulin or retinol-binding protein, which are freely filtered at the glomerulus and reabsorbed in health by the proximal tubules. Albumin makes up little of the measured proteinuria, in contrast to glomerular diseases, and thus it is of no use relying only on albumin-to-creatinine ratios, commonly used in certain laboratories, but in addition measuring protein-to-creatinine ratios. Imaging of the kidneys may reveal them to be enlarged with increased echogenicity on ultrasound scanning. Gallium-67 isotope scan may reveal strong renal uptake but is by no means specific, and should not be relied upon as a diagnostic tool.

Suggested investigations in cases of TIN are shown in Table 29.4. Further tests may be required in specific cases based on the suspected underlying diagnosis.

Pathology

Regardless of the aetiology of TIN, there are a number of common pathological features. Acutely, there is oedema, tubular injury and a cellular infiltrate (Fig. 29.1). This generally consists of lymphocytes, CD4+ and CD8+ T cells and B cells, plasma cells, macrophages, and occasional granulocytes and NK cells. Granulomata may be present, as are eosinophils in certain forms of TIN (commonly secondary to drugs). Chronically, there is persistent cellular infiltration, tubular atrophy, and interstitial fibrosis. Progression to chronicity with accompanying fibrosis may be rapid, occurring within weeks. Alternatively, the inflammation may resolve spontaneously, without consequence. Many series have found a correlation between the degree of interstitial infiltrate and the severity of renal impairment, and between the degree of infiltration and the long-term outcome, although others have not. Factors determining the outcome of interstitial inflammation, with repair and resolution or atrophy and fibrosis, remain poorly defined.
Table 29.4  Suggested investigations in TIN

<table>
<thead>
<tr>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea, creatinine, electrolytes, calcium, phosphate, uric acid, chloride, bicarbonate full blood count including eosinophil count</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunology</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCA, ANA, dsDNA, ENA RhF, cryoglobulins, immunoglobulins, serum complement ACE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipstick</td>
</tr>
<tr>
<td>Microscopy (Hansel's stain for eosinophils)</td>
</tr>
<tr>
<td>Spot electrolytes, osmolality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spot protein: creatinine ratio (or 24-hour collection for protein, including low molecular weight proteins)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound scanning</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; ANA, anti-nuclear antibodies; ANCA, anti-neutrophil cytoplasm antibodies; ENA; extractable nuclear antigens; RhF, rheumatoid factor.

Fig. 29.1  Photomicrograph of renal biopsy section from a patient with tubulo-interstitial nephritis and uveitis syndrome (TINU), showing a typical pattern of inflammation in the interstitium, with a heavy mononuclear cell infiltrate. There is loss of normal tubular architecture, with tubular atrophy and dilatation, large casts within the tubular lumens and interstitial expansion and oedema. The glomeruli are uninvolved. (H and E ×75).
From human studies and animal models, tubular damage is known to occur through activity of the different effector arms of the immune response. It may be due to antibody or immune complex deposition, but is more commonly due to cellular immunity in the form of delayed type hypersensitivity reactions and cytotoxic effector cells. Antibodies may directly bind the tubular basement membrane (TBM), as in anti-TBM disease, or may be directed against other unknown antigens in the tubulointerstitium. Such antigens may be a structural part of the tubule, may be secreted by it or may be part of the urinary filtrate. In the rare form of antibody-mediated TIN, there is usually linear deposition of immunoglobulin on the TBM, and in immune complex-mediated TIN there are granular deposits.

Delayed-type hypersensitivity (DTH) reactions and granulomata are found in TIN (Fig. 29.2), but in few of them is the T cell antigen known. Both CD4+ and CD8+ T cells are found, in varying proportions. Some are in an activated state, as evidenced by expression of CD25 (interleukin (IL)-2-receptor α chain) and major histocompatibility complex (MHC) class II antigens on their cell surface. Recent data have demonstrated an extensive network of interstitial dendritic cells, capable of sampling tubular proteins and presenting antigen to infiltrating T cells, which may be implicated in development of chronic TIN.

In addition, it has been suggested that infection with Epstein-Barr virus (EBV) may be a cause of chronic ‘idiopathic’ interstitial nephritis (and see Sjögren’s syndrome below). EBV viral DNA has been found in the tubulo-interstitium in renal biopsy specimens from patients with chronic ‘idiopathic’ TIN, and the EBV receptor (CD21) was identified on proximal tubular cells. Viral particles were not identified in drug-related TIN. These data suggest a causal role for EBV in inducing or perpetuating chronic interstitial inflammation.

**Rheumatological conditions with TIN**

**Systemic lupus erythematosus (SLE)**

In patients with SLE, TIN generally occurs in association with glomerular lesions. TIN may be seen in any of the World Health Organization (WHO) classes of lupus nephritis, although it occurs more commonly in grades III and IV, and in patients with more active disease. There are occasional reports of patients with SLE in whom TIN occurs in isolation, and in whom it is responsible for either acute or chronic renal failure. These patients generally have active disease, with positive anti-nuclear antibodies (ANA) and DNA binding. One reported patient was asymptomatic from their lupus, and had renal tubular acidosis as the only manifestation of disease. Functional disturbances in tubular function are common in patients with SLE, with up to 80% having some abnormality of tubular concentrating ability, urinary acidification or proximal tubular cell reabsorptive capacity. There is no clear correlation between the functional tubular abnormalities and renal histology.

Immune complex deposits along the TBM on renal biopsy are found in approximately half the cases of lupus nephritis. Deposits are similar to those found elsewhere in SLE, that is to say they consist of IgG, IgM, C1q, C3, C5–9 and, rarely, IgA. However, there may be greater variability in the composition of deposits in the interstitium.
Interstitial capillary immune deposits are almost exclusive to SLE. There is a report of linear deposition of IgG, suggesting anti-TBM antibodies, in association with TIN in a child with SLE. The severity of interstitial inflammation does not generally correlate with the extent of tubulo-interstitial deposits. Thus, cellular mechanisms in addition to antibody

Fig. 29.2 (a) Photomicrograph of renal biopsy section from a patient with tubulo-interstitial nephritis, stained for macrophages with anti-CD68 mAb. There is a marked increase in macrophage numbers, with widespread infiltration throughout the interstitium. (H and E x190). (b) Photomicrograph of renal biopsy section from a patient with tubulo-interstitial nephritis stained for the presence of CD3, a pan T cell marker. There is a heavy, patchy infiltration of T cells surrounding the tubules, with evidence of tubular cell damage (tubulitis). (H and E x190).
deposition may operate to induce tubular damage. Recent work has highlighted Th2 and Th17 cytokine production from interstitial T lymphocytes in patients with class III–V lupus nephritis. In one case of SLE-related TIN, significant numbers of interstitial mast cells were also found.

**Treatment and outcome**

In cases of isolated SLE-related TIN, treatment has been variable, and the number of reports is too few to allow specific recommendations to be made. In most patients, medium to high doses of corticosteroids were used, sometimes with additional immunosuppression, and this led to improvement of renal function in over half. In other cases no immunosuppressive treatment was given and there was an improvement in renal function, although not back to normal. One patient was monitored for 3 years and followed a relatively benign course, with no sign of renal deterioration. In cases of TIN secondary to glomerular disease, treatment options are dictated by the severity of glomerulonephritis (GN) and have been reviewed elsewhere.

**Sjögren’s syndrome**

Sjögren’s syndrome (SS) is an autoimmune condition in which there is cellular infiltration of the exocrine glands, notably the salivary and lacrimal glands, giving rise to the characteristic clinical features. The condition may occur in isolation (primary SS) or in association with other autoimmune diseases, such as rheumatoid arthritis or SLE (secondary SS).

Renal involvement is well recognized but infrequent, and is often subclinical, with between 2% and 26% of patients developing overt disease. Renal impairment is generally mild, but may be severe and result in acute or chronic renal failure. Urinary abnormalities may be minor, with occasional leucocytes and modest proteinuria. The most common histological abnormality is TIN with a predominant lymphocytic infiltrate, consisting mostly of T cells. Tubular atrophy, nephrocalcinosis, interstitial oedema and fibrosis occur to variable extents. By contrast, glomerular changes are rare. Latent tubular abnormalities are reported to occur in 20–85% of patients. Tubulo-interstitial immune deposits have been reported, although they are generally absent and areas of tubular atrophy and fibrosis appear to coincide with the immunoglobulin deposits, suggesting a possible aetiological role for the antibodies in tubulo-interstitial inflammation. Rarely, immune complex-mediated GN may also occur, with membranous or membranoproliferative types predominating.

Functional renal tubular defects, such as renal tubular acidosis, nephrogenic diabetes insipidus and Fanconi’s syndrome may occur in up to 50% of cases. Their presence does not appear to correlate with the histological findings, and may be subclinical. They tend to be more common in younger patients with chronic disease and impaired renal function. The most common tubular abnormality, and a sensitive indicator of renal involvement in SS, is a defect in concentrating ability, which occurs in up to 80% of patients. Renal tubular acidosis may be distal or proximal, with the former being more common. The patients are generally asymptomatic, and the diagnosis is established by finding hyperchloraemic acidosis with hypokalaemia. In about 30% of cases the defect is latent and only apparent after an acid-load test. Less often, the biochemical abnormalities...
may lead to symptoms that are the presenting features of undiagnosed SS, such as hypokalaemic paralysis. Hypergammaglobulinaemia itself does not appear to be sufficient to induce renal tubular acidosis; however, specific anti-tubular antibodies may be able to induce such tubular defects, localizing to particular tubular segments. Alternatively, the interstitial cellular infiltrate may be responsible, as is thought to be the case in the salivary and lacrimal glands.\textsuperscript{30}

An aetiological role for EBV has been suggested in this condition. Viral DNA has been found in the salivary glands, peripheral blood mononuclear cells and renal tubules in patients with SS, along with the viral cell receptor CD21.\textsuperscript{31} EBV DNA has also been found in other cases of chronic TIN, suggesting that there may be a more generalized role for this virus in initiating or perpetuating interstitial inflammation.

**Treatment and outcome**

TIN resulting in mild stable renal impairment may be left untreated without further deterioration. Treatment of isolated distal renal tubular acidosis is with sodium bicarbonate and potassium supplements. Renal tubular acidosis as well as interstitial inflammation may respond to long-term low-dose steroid therapy.\textsuperscript{32} Higher doses of steroids, such as pulsed methylprednisolone, may be required in cases showing a rapid evolution to uraemia. In some cases, an additional immunosuppressive agent such as cyclophosphamide has been used, with marked improvement in renal function. Despite resolution of interstitial inflammation following treatment, tubular fibrosis appeared to develop in areas associated with TBM immune deposits.\textsuperscript{27} Secondary SS in association with SLE is generally treated with drug regimens appropriate for SLE.

**Overlap syndromes/mixed connective tissue disease (MCTD)**

A rheumatological overlap syndrome with features of SLE, systemic sclerosis and polymyositis, and characterized by the presence of extractable nuclear antigens (ENA) was first described by Sharp in 1972.\textsuperscript{33} Its definition has undergone some revision, and it may represent a transitional syndrome, which polarizes to one or other condition with time. Thus, MCTD is now more properly identified, in association with antibodies to U1-RNP, in patients with synovitis, myositis, Raynaud’s phenomenon, hand oedema and acrocyanosis.\textsuperscript{24} Renal involvement in this condition is more common than originally thought, occurring in up to a third of cases. Glomerular and vascular pathology predominate (mimicking that in SLE and scleroderma respectively), with membranous GN being the most common glomerular lesion. In one series, up to 20\% of patients had evidence of interstitial disease, although this was often secondary to glomerular lesions.\textsuperscript{34} TIN has been also reported, although of less severity than lesions found in SLE.\textsuperscript{35} Serological studies do not predict those with renal disease. Treatment has generally been with steroids, as used for SLE.

**Tubulo-interstitial nephritis and uveitis (TINU) syndrome**

In 1975, Dobrin et al. described two children who presented with acute renal failure secondary to eosinophilic interstitial nephritis.\textsuperscript{36} They also had bilateral uveitis, bone marrow granulomas, hypergammaglobulinaemia and an acute phase response. No evidence for any aetiological agent was found so it was proposed that this was a new
syndrome, appropriately termed tubulo-interstitial nephritis and uveitis (TINU).\textsuperscript{36} Since then there have been several reports of the association of interstitial nephritis and uveitis,\textsuperscript{37,38} although not always with granulomata. TINU remains a diagnosis of exclusion, as other systemic conditions may be associated with interstitial nephritis and uveitis, for example sarcoidosis and Wegener’s granulomatosis (WG). Whether this syndrome represents a \textit{form fruste} of sarcoidosis, or is truly a separate entity, remains to be clarified. The uveitis may occur at any time in relation to the nephritis, and has a tendency to relapse, unlike the tubulo-interstitial lesions.\textsuperscript{38} Females are more commonly affected. Early reports tended to be mostly of children, although it is now apparent that all ages are susceptible.

Non-specific symptoms of lethargy, myalgia, anorexia, weight loss and fever are common. Urinary abnormalities consist of proteinuria, leucocyturia, and tubular defects leading to glycosuria, aminoaciduria and impaired concentrating ability.\textsuperscript{38} Hypergammaglobulinaemia and an acute phase response seem to be universal. In some cases autoantibodies are found, including rheumatoid factors, ANA and more recently anti-neutrophil cytoplasm antibodies (ANCA).\textsuperscript{39} Histological changes consist of interstitial cellular infiltration, with tubular atrophy and fibrosis (Fig. 29.1). Immune deposits along the TBM are generally absent. The cells are mostly T lymphocytes, in an activated state, but eosinophils occasionally predominate, as originally described.\textsuperscript{36} A genetic predisposition is likely, as TINU has been reported to occur in twins, and a suggestion of human leucocyte antigen (HLA)-disease linkage has been made, with certain HLA-A, -B, -DR and -DQ alleles demonstrating disease associations.\textsuperscript{40}

Associations with infectious agents including chlamydia have been reported. There is also an animal model in which both uveitis and granulomatous TIN are produced following inoculation with mycoplasma-like organisms (MLO) obtained from patients with chronic uveitis.

**Treatment and outcome**

Renal recovery is the general rule, often without treatment. In a number of case reports, corticosteroids were given and recovery was ascribed to the treatment. The uveitis generally requires therapy with topical or systemic corticosteroids, and has a tendency to follow a relapsing remitting course.

**Sarcoidosis**

Sarcoidosis is a chronic multi-system granulomatous disorder, more common in young black women, with a variable presentation and unknown aetiology. Impaired renal function in sarcoidosis is rare, occurring in only 1–2\% of patients. A much higher incidence of renal involvement, of up to 25\%, is found in autopsy series. Renal involvement is generally due to nephrocalcinosis, nephrolithiasis and dehydration consequent to hypercalcaemia. Hypercalcaemia and hypercalciuria occur in 10\% of patients, and are associated with reversible impairment in renal function. Nephrocalcinosis occurs in up to a third of those with hypercalcaemia.

However, interstitial nephritis in the absence of hypercalcaemia was first described by Berger and Relman in 1955 and has been reported in a number of patients
subsequently. The incidence of interstitial nephritis varies from 1.3% to 40% depending on the series. Glomerular disease and vasculitis may occur in sarcoidosis, although they are more rare than interstitial nephritis. Renal granulomas, containing epithelioid and giant cells, are common and often surrounded by an inflammatory infiltrate consisting mostly of lymphocytes and plasma cells (Fig. 29.3). The granulomas are typically in the cortex, but can occur throughout the renal parenchyma. The lymphocytes are mostly CD4+ T cells, mirroring those found in other sarcoid granulomas. No immune deposits are seen. In one series of patients with granulomatous interstitial nephritis, only 7% had normal renal function and 45% had severe renal failure (glomerular filtration rate (GFR) <20 ml/min).

Presentation may be following routine renal function testing, or with polyuria or haematuria. More commonly it follows other systemic symptoms of sarcoidosis (see Table 29.5). Patients may have mildly active urinary sediment, proteinuria, tubular defects such as reduced concentrating ability, and renal impairment. Levels of serum angiotensin converting enzyme may be normal, as can gallium scintigraphy, although it has been found to be positive in some cases of active granulomatous nephritis. Patients with sarcoidosis and granulomatous interstitial nephritis tend to be older male patients, with no racial bias.

**Treatment and outcome**

In patients with severe renal failure, corticosteroid therapy results in significantly improved renal function in 85% of cases. In some instances dialysis-dependent patients may recover independent renal function. Up to 28% relapsed in Simonsen's
series, and progressed towards end-stage renal disease. Relapse has also been noted in a renal transplant patient despite immunosuppression, and in other patients on cessation or rapid reduction of steroids. Treatment generally consisted of 60 mg of prednisolone, lasting for between 6 weeks and 4 years. In a few reports, steroid-sparing agents were tried, with apparent success. In some relapses re-institution of treatment resulted in improved renal function. In those with moderately impaired function (GFR 20–80 ml/min), steroids had a less dramatic effect with 65% improving and about a third left with unchanged renal function. It appears that those treated with lower doses of steroids fared worse. Steroid therapy is also beneficial in reversing tubular dysfunction, manifested by diabetes insipidus and renal glycosuria. In patients undergoing repeat biopsies following steroid therapy, granulomas and mononuclear infiltrates had regressed but there may be evidence of fibrosis and scarring. This could explain why many patients who respond to steroid therapy have residual renal impairment up to 30 months later. Thus, it would seem advisable to treat patients with a prolonged course of moderate to high doses of steroids in the first instance, and gradually taper the dose, while remaining vigilant for signs of relapse. In cases where steroids are contraindicated or need to be minimized to prevent adverse drug events, chlorambucil or methotrexate have been used. More recently, success has been achieved using tumour necrosis factor (TNF) blockade with infliximab, but not etanercept and further studies are needed to better define the optimum treatment protocols with TNF antagonism.

**Systemic vasculitis and TIN**

ANCA are serological markers of pauci-immune GN, whether it is limited to the kidney or associated with other systemic manifestations as in WG, microscopic polyangiitis

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**Table 29.5 Clinical features and investigations in patients with sarcoid granulomatous interstitial nephritis**

<table>
<thead>
<tr>
<th>Clinical features (in descending order of frequency)</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hilar lymphadenopathy</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
<td>Haematuria</td>
</tr>
<tr>
<td>Fever</td>
<td>Granular casts</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Renal glycosuria</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Proteinuria (&lt;2 g/24 hours)</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td>Sterile pyuria</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Concentration defects, urine specific</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>gravity &lt;1.007</td>
</tr>
<tr>
<td>Rash</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>Sinus involvement</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from.

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(MPA) or Churg–Strauss syndrome (CSS). Interstitial inflammation in cases of pauci-immune GN is common, and this may develop into granulomatous TIN, as seen in WG and CSS (along with eosinophilic infiltration). Isolated interstitial nephritis associated with ANCA is recognized but uncommon. In one series, 11% of patients with WG and MPA had evidence of interstitial nephritis without glomerular involvement. Four of these six cases had ANCA and in none of them was the clinical diagnosis considered to be TIN. Cases of severe eosinophilic TIN in association with ANCA, but lacking sufficient criteria for a diagnosis of CSS, have also been reported. Additionally, ANCA have been reported in some patients thought to have TINU. In our series of patients presenting with acute TIN, two have ANCA (representing 10%), one of which was associated with anti-myeloperoxidase (MPO) antibody. Neither had features of systemic vasculitis, nor have they gone on to develop them. Thus, ANCA may also be associated with TIN, possibly as a non-specific autoimmune phenomenon, without evidence of vasculitis. A severe neutrophil-predominant TIN may occur in patients treated with azathioprine presumably as a reaction to the drug, often mimicking vasculitic relapse, and only diagnosed on renal biopsy.

Treatment and outcome

Treatment of ANCA-associated systemic vasculitides has been extensively covered elsewhere. Isolated TIN associated with systemic vasculitis has generally been treated with similar, although less intensive regimens, with steroids alone in some cases, but combined with additional immunosuppressive treatment in more severe cases.

**Essential mixed cryoglobulinaemia (EMC)**

EMC is characterized by circulating immunoglobulins capable of precipitating in the cold. In type II ECM the immunoglobulins are a mixture of a monoclonal IgM rheumatoid factor (RF) and polyclonal IgG bound to the RF. Many cases are associated with chronic hepatitis C infection in Southern Europe, although this may be less common in Northern Europe where the disease is still mostly idiopathic. In EMC, the most common renal lesion is a mesangiocapillary GN, and this is often accompanied by interstitial inflammation. In some cases, immune complex deposits containing IgG, IgM and C3 are extensive and are associated with progressive chronic damage. Interstitial infiltration by predominantly CD8+ T cells is also found, associated with tubular injury. However, in many cases these changes more likely reflect the glomerular and vascular damage. In cases associated with hepatitis C antiviral therapy is required, whereas addition of plasmapheresis, steroids and cytotoxic agents or rituximab has been required in some cases of severe renal involvement.

**Relapsing polychondritis (RP)**

RP is a rare autoimmune disease in which cartilaginous type II collagen is the primary target of immune attack. It has clinical diagnostic criteria and may co-exist with other autoimmune diseases and in some cases is associated with positive ANCA serology. There may be renal involvement in up to 22% of patients, in which glomerular lesions predominate. However, TIN has been also been reported, although how much this is due to co-existent autoimmune pathologies is unclear.
The number of cases reported are small, and they have been treated with steroids alone or in combination with cytotoxic agents.

**Conclusions**

TIN may occur in a number of systemic diseases, albeit infrequently, and lead to acute or chronic renal impairment. It is a diagnosis that requires a high index of suspicion and a confirmatory renal biopsy. It may be associated with a range of functional tubular abnormalities, which are often subclinical in nature. The inflammatory reaction generally responds to immunosuppressive treatment with corticosteroids, although this may not prevent subsequent tubular atrophy and interstitial fibrosis. Little is known regarding the immunological stimulus that triggers this condition, or the factors involved in progression or resolution.

**Take home points**

1. Renal involvement may occur in a number of rheumatological conditions. It may be asymptomatic and its timely diagnosis requires clinical vigilance.
2. Urinalysis should be performed regularly in all patients with rheumatic disease and proteinuria quantified by spot protein-to-(not albumin) creatinine ratio.
3. Renal biopsy remains the only definite way to diagnose TIN and in experienced hands is a safe procedure.
4. Treatment of TIN associated with rheumatic disease has generally relied on corticosteroids, with other therapy being dictated by concurrent glomerular lesions. These recommendations come from small cohort series and not from randomized studies.
5. The factors regulating resolution or progression of disease remain poorly defined.

**Acknowledgement**

We are grateful to Dr T. Cook for providing the histopathology specimens.

**References**

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest

   * Contemporary analysis of TIN aetiology.
* Detailed account of disease pathophysiology.


** New insight into the role of the renal dendritic cell network.


* Novel method analyzing the immunophenotype of infiltrating leucocytes.


* Modern approach to management of renal lupus.


* Original description of the TINU syndrome.


* Modern management of ANCA-associated vasculitis.


** Different patterns of cryoglobulinaemia between Northern and Southern European.

Chapter 30

Management of gout in the patient with renal disease

Philip Courtney and Michael Doherty

Introduction

Gout is a true crystal deposition disease caused by formation of monosodium urate (MSU) crystals in and around peripheral synovial joints. MSU crystal deposition initially favours lower more than upper limb joints, and particularly targets the first metatarso-phalangeal joint (MTPJ) and small joints of feet and hands. MSU crystals are needle-shaped, hard, highly inflammatory agents with a high negative surface charge. Shedding of MSU crystals into the joint space can trigger acute attacks of florid synovitis (acute gout), and hard impacted concretions of crystals (‘tophi’) can cause pressure damage to cartilage and bone, leading to chronic arthritis (chronic tophaceous gout) and sometimes clinically evident tophi in subcutaneous tissues and bursae.

The unadjusted crude prevalence of gout in adults is around 2% (1). However, it is more common in men (4–5:1) and increases with age, reaching a maximum prevalence of around 7% in men over age 75 (Fig. 30.1). Gout is the most common inflammatory joint disease in men and the most common inflammatory joint disease in older women. Epidemiological studies confirm that over the past 30–40 years the incidence and prevalence of gout has increased in many countries, especially for primary gout in older men. Elevation of serum uric acid (SUA) levels, with accompanying high levels of tissue urate, is the key prerequisite for MSU crystal deposition. The increasing prevalence of end-stage renal failure is a contributing factor to this observed increase in gout and hyperuricaemia, with almost three-quarters of patients seen in a hospital setting with gout having renal impairment. The management of gout in patients with renal disease is often challenging because:

- most drugs recommended for both acute and chronic gout are contraindicated in renal failure requiring safer ‘renal friendly’ drugs and novel strategies to control gout and prevent disabling attacks
- the very high SUA levels that often result from renal failure often accelerate the speed of MSU crystal formation and lead to more rapid appearance of tophi, more extensive deposition and more frequent and severe acute attacks
- clinical presentation is often atypical, for example initial acute attacks in upper rather than lower limb, and presentation with discharging tophi without preceding recurrent acute attacks.
Furthermore, hyperuricaemia and gout themselves may cause renal damage through deposition of urate crystals and microtophi in the renal interstitium, uric acid crystal deposition within tubules and an increased incidence of uric acid and calcium phosphate renal stones.\(^9\),\(^10\)

**Uric acid metabolism and risk factors for gout**

Approximately two-thirds of the body’s uric acid pool is derived from endogenous breakdown of purines, the remaining one-third usually coming from dietary intake of purines (Fig. 30.2).\(^11\) The kidney is the main route of excretion (c. two-thirds), although approximately one-third of uric acid is excreted into the gut where colonic bacteria break down the less soluble urate into more soluble allantoin (unlike man, bacteria possess the enzyme uricase to do this).

Gout is a common complex disorder that results from interaction between genetic, constitutional and environmental risk factors (Table 30.1).\(^1\),\(^11\) Monogenic disorders that result in overproduction of uric acid via enzyme defects in uric acid metabolism (e.g. Lesch-Nyhan syndrome) are exceptionally rare. Common primary gout in men does show strong familial predisposition, although the precise genetic basis remains unknown.\(^11\),\(^12\) Several genes relating to uric acid handling in the proximal tubules have been identified including URAT1 and SLC2A9 (GLUT9), and certain polymorphisms in these genes have been associated with an increased risk of hyperuricaemia and gout through relative renal inefficiency in eliminating urate.\(^1\),\(^11\),\(^13\)–\(^15\) Obesity is a risk because of the higher turnover of purines that accompanies an increase in body mass. Recent studies have confirmed specific dietary factors that also confer either a positive or negative risk.\(^16\)–\(^20\) For example, higher intakes of red meat, fructose and beer (beer is rich in the purine guanosine) independently associate with increased risk, whereas higher intakes of coffee, low-fat dairy products and vitamin C are each
Apart from obesity, each element of the metabolic syndrome (hypertension, insulin resistance, hyperlipidaemia) independently reduces the efficiency of renal urate excretion. Conversely, treatment of each of these will result in reduction of SUA.\textsuperscript{21} Other than renal disease itself, many drugs reduce the efficiency of renal urate clearance, the most important being diuretics.\textsuperscript{22} Cyclosporine is an example of a drug that is sometimes used in patients with renal impairment (transplant patients), which reduces renal urate clearance,\textsuperscript{23} and low-dose aspirin is given to many

Table 30.1 Risk factors for gout

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Predominantly related to renal inefficiency to excrete urate (rarely enzyme disorders resulting in urate overproduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Dietary factors – high purine intake (e.g. red meat, seafood)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Alcohol (beer, spirits)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Drugs that reduce renal excretion of urate (e.g. diuretics, cyclosporine)</td>
</tr>
<tr>
<td>Ageing</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Chronic lead poisoning</td>
<td></td>
</tr>
</tbody>
</table>
renal patients with cardiovascular disease and also contributes to hyperuricaemia. Ageing is a significant predisposing factor, possibly as a result in part to age-related reduction in renal function but also to the increased prevalence of osteoarthritis (OA). Cartilage changes in OA may locally encourage MSU crystal formation in people with high urate levels, perhaps explaining the very common involvement of the 1st MTPJ – the target site for OA in the foot.

**Diagnosis**

Although chronic elevation of SUA is a key risk factor for gout it is unhelpful for diagnosis. This is because:

- many people are hyperuricaemic but never develop gout
- some people with gout have normal or even low SUA levels at presentation, especially during an acute attack (SUA is a negative acute phase reactant and lowers as CRP rises).

In a patient with classic acute attacks affecting the 1st MTPJ the diagnosis can be made with some confidence. However, with less typical presentations definitive diagnosis requires demonstration of MSU crystals by polarized light microscopy in the aspirate from a joint, bursa or tophus. Typically, MSU crystals are long needle-shaped crystals, showing strong light intensity and negative birefringence. Joint aspiration is most commonly performed during an acute attack, although MSU crystals can still be identified in a high proportion of fluids aspirated from un-inflamed joints during an inter-critical period between attacks.

**Pathophysiology**

For MSU crystals to form, the ionic product of sodium and urate must be above the saturation point for crystal formation. Importantly, this saturation point for MSU crystal formation is also the therapeutic target for urate lowering therapy (ULT). MSU crystals preferentially form within cartilage and fibrous tissues where they are relatively protected from contact with inflammatory mediators. However, if shed from their site of origin into the joint cavity, MSU crystals are quickly phagocytosed by monocytes and macrophages. This is followed by activation of the NALP3 (cryoprin) inflammasome, release of interleukin (IL)-1β and other cytokines, and subsequent infiltration of neutrophils and a florid inflammatory reaction. Acute gout can be triggered by intercurrent illness or surgery, because being a negative acute phase reactant the SUA level is lowered (through temporary increased renal excretion) and this partially dissolves existing MSU crystals, making them smaller and thus more easily shed from their cartilage origin. The same explanation is suggested for the observed provocation of attacks after initiation or dosage increase of ULT.

**Clinical presentation**

The usual initial presentation of gout is with rapidly developing acute inflammatory monoarthritis. The 1st MTPJ is the characteristic target joint, but other joints frequently
affected include the midfoot, ankle, knee, wrists, finger joints and elbow (Fig. 30.3): axial joints (shoulders, hips, spine) are rarely affected. The rapid development of severe pain (‘worst ever’—on the same level as childbirth or renal colic) reaching a maximum within 6–24 hours of onset and resolving spontaneously over several days to 2 weeks is almost pathognomonic of crystal arthritis. Although most attacks are mono-articular, the elderly and patients with renal disease are at increased risk of oligo or polyarticular attacks. Simultaneous involvement of several joints is more likely to be associated with systemic upset and fever. Other than the acute attack, patients may present with more chronic joint symptoms (pain, stiffness, swelling), which affect the same joints as acute attacks. Some patients present with tophi, as unexplained painless swellings or as intermittently inflamed painful lumps mainly localized over extensor surfaces of feet, knees, hands and elbows. White to yellow discoloration beneath the skin may permit distinction from rheumatoid nodules (MSU crystals are white). If left untreated, it may progress with recurrent acute attacks and eventual development of chronic symptoms and joint damage. Tophi may break down and discharge pus and white material, inevitably leading to consideration of infection (Fig. 30.4).
Management

The following considerations are essential to successful management: 7, 8

- patient education and information access about gout and its treatment is of paramount importance
- management must be individualized to the patient, taking into account risk factors, co-morbidity other than renal impairment, and the severity of their gout
- for chronic management, lifestyle modification applies equally to patients with renal disease as to those with primary gout. The main considerations are reducing body mass index (BMI) if overweight, adjusting diet to reduce high purine intake and reducing beer consumption (moderate wine intake is not a risk for hyperuricaemia). Withdrawal or dose reduction of diuretics or other relevant drugs is sometimes possible.

Treatment of acute gout in patients with renal failure

The following treatments should be considered: 6–8

- **local ice-packs**: these are safe and often provide some relief of the extreme pain associated with the acute attack
- **aspiration and injection of long-acting glucocorticosteroid**: this is the best option for a mono-articular attack in a hospital setting. 7, 8 Aspiration rapidly reduces the high intra-articular pressure that causes the extreme pain of acute gout, and the steroid
suppresses acute inflammation and prevents fluid re-accumulation. Obtaining synovial fluid additionally permits confirmation of the correct diagnosis. If septic arthritis is a possibility (e.g. because of admission for intercurrent infection or following surgery), the fluid can also be sent for gram stain and culture. Sepsis, however, is more subacute and worsens from day to day – only crystal synovitis produces such rapid onset of severe inflammation. Therefore, if the clinical picture is crystal synovitis, the steroid should be injected at the first aspiration and not at a second aspiration 48 hours later after a negative culture has returned. In the uncommon instance of simultaneous gout and infection in the same joint, as long as the synovial fluid is examined for bacteria and treatment subsequently started within 48 hours, the steroid injection will have done no harm (in fact it will have protected the joint from damage by inhibiting auto-destructive catalytic systems).

◆ intramuscular injection of glucocorticosteroid (or adrenocorticotropic hormone (ACTH)): this may be considered for polyarticular attacks or when the affected joint is not readily amenable to aspiration (e.g. a mid-tarsal attack). ACTH has the double action of increased release of endogenous steroid plus inhibition of melanocortin 3 receptor (important in neutrophil-driven inflammation) and is often rapidly effective. A short course of oral steroid is sometimes used in the same circumstances, especially in general practice.

◆ oral colchicine: this should be used cautiously in low dose (e.g. 0.5 mg twice daily) in patients with renal impairment, because of increased toxicity, and at this low dose it may be insufficient to achieve a response. If a quick acting non-steroidal anti-inflammatory drug (NSAID) is the most common treatment for acute gout in general practice, but these drugs are contraindicated in patients with renal disease. Currently, there is considerable interest in the use of anti-IL1 drugs that effectively block the inflammasome as a novel treatment for acute gout. One small uncontrolled study has reported success at treating acute gout with the commercially available IL-1 receptor antagonist anakinra, given by subcutaneous injection of 100 mg daily for 3 days.

Rilonacept is an anti-IL1β antibody and one recent placebo controlled trial has shown efficacy at reducing chronic crystal induced inflammation and frequency of acute attacks when given by weekly subcutaneous injection. Other anti-IL1β agents with even longer duration of benefit (up to 8 weeks from one injection) are in development, and such treatments could have a future role in treating acute attacks of gout, or for prophylaxis during initiation of ULT, in patients with renal impairment who cannot take NSAIDs or colchicine. Prophylactic therapy of gout is a common concern when initiating ULT as approximately two-thirds of patients with renal impairment treated with allopurinol experience a flare during the first year of therapy. It is recommended that gout should be in remission before commencing ULT, but once started it should not be stopped if there is an acute attack of gout.

**ULT in patients with renal impairment**

The therapeutic target of any ULT is to reduce the SUA below the saturation point for urate crystal formation, thereby preventing formation of new crystals and encouraging
dissolution of existing crystals.\textsuperscript{7,8} The SUA that equates with this is c. 360 μmol/l (6 mg/dl).\textsuperscript{7} However, the lower the SUA is below this level, the faster the dissolution of crystals and tophi and the sooner the patient is ‘cured’ with no further ability to have acute attacks.\textsuperscript{36} This in part is why the British guidelines recommend a stricter therapeutic target of <300 μmol/l, which is the median level in UK men.\textsuperscript{8} The longer the duration of gout and the greater the crystal load prior to commencing ULT, the longer it takes to reach ‘cure’.\textsuperscript{37}

When commencing ULT it is advisable to start at a low dose and to titrate upwards until the therapeutic target has been achieved. This ensures that the patient is on the lowest dose of ULT that they need. In addition, slower lowering of SUA may reduce the risk of provoking flares, the less rapid reduction in MSU crystal size allowing surrounding cartilage and connective tissue to accommodate and ‘close down’ on the crystals, reducing the tendency for crystal shedding. There is no specific agreed titration regimen, but incremental increase every 3–4 weeks is commonly undertaken.

In patients with renal impairment the following ULT options are available.

Allopurinol

This is the usual first-line ULT to consider for treatment of gout.\textsuperscript{5–8,36} It is a purine non-specific inhibitor of xanthine oxidase that converts the following two reactions at the end of purine breakdown:

\[
\text{hypoxanthine} \rightarrow \text{xanthine} \rightarrow \text{uric acid}
\]

Allopurinol competitively inhibits the oxidized form of xanthine oxidase, this action converting allopurinol to its active metabolite oxypurinol, which inhibits the reduced form of xanthine oxidase.\textsuperscript{7,8} The usual dose range is 100–900 mg/day (up to 600 mg/day in some countries), and the therapeutic target can usually be reached in patients with normal renal function at doses between 200 and 400 mg/day.

Because oxypurinol is excreted through the kidney, renal impairment may result in toxicity. Therefore, allopurinol should be given in reduced dose to patients with renal disease.\textsuperscript{7,8,38} The starting dose in renal patients is 50 mg and the dose is then titrated up with careful monitoring of renal function. Detailed formulae are available incorporating GFR, BMI and ethnic origin to help with dose calculation\textsuperscript{38} but the following gives some idea of the dose reductions required:

<table>
<thead>
<tr>
<th>GFR (ml/min)</th>
<th>Usual dose and frequency of allopurinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>200–300 mg daily</td>
</tr>
<tr>
<td>60–80</td>
<td>100–200 mg daily</td>
</tr>
<tr>
<td>30–60</td>
<td>50–100 mg daily</td>
</tr>
<tr>
<td>15–30</td>
<td>50–100 mg alternate days</td>
</tr>
<tr>
<td>on dialysis</td>
<td>50–100 mg weekly</td>
</tr>
</tbody>
</table>
Unfortunately, in patients with renal disease it may not be possible to reach the therapeutic target because of this dose restriction. The other major concern is the rare allopurinol hypersensitivity reaction, which is a form of DRESS (Drug Rash or Reaction with Systemic Symptoms) syndrome and may be severe and even fatal. This usually develops in the first 3 months of treatment and is almost confined to people with renal impairment. Less severe reactions (skin rash without other upset) are also more common in patients with renal impairment. Such patients may be considered for allopurinol desensitization, but this is time-consuming and not always effective.  

Another potential disadvantage of allopurinol in patients with renal disease is the interaction with azathioprine, which is commonly used for prevention of renal transplant rejection. Azathioprine is metabolized by xanthine oxidase to its marrow-depressant metabolite 6-mercaptopurine so interaction can have serious consequences. There is no interaction, however, between allopurinol and mycophenolate mofetil.

**Febuxostat**

Febuxostat is a recently introduced (2010) non-purine highly specific inhibitor of xanthine oxidase and is likely to represent a major advance in ULT for patients with renal impairment. It provides long-lasting inhibition of both the oxidized and reduced form of xanthine oxidase and is metabolized by the liver (CYP - cytochrome p450 system). Because it does not undergo renal excretion there is no need for dose adjustment and no apparent risk of specific toxicity in patients with reduced renal function. Febuxostat is approved by NICE in the UK as ULT to consider in patients who are intolerant to, or who have contraindications (mainly severe renal impairment) to, allopurinol. It is available at a starting dose of 80 mg, which can be increased, if required, to the second, maximum dose of 120 mg daily. Although it is likely to be a very useful drug, especially in patients with renal impairment, it has the following caveats:

- **restricted dose options (80 or 120 mg):** this limits the amount of titration steps and the ability to fine-tune the dose to the individual
- **requirement of prophylaxis for 6 months following initiation:** both the 80 and 120 mg doses are highly efficient at lowering SUA and therefore provoke acute attacks. Unfortunately, patients with renal impairment cannot take oral NSAID and even low doses of colchicine (0.5 mg twice daily) may be problematic
- **lack of sufficient efficacy in some patients:** in published trials only 60–70% of patients on the full dose of febuxostat (120 mg daily) reached the therapeutic target of <360 μmol/l
- **concerns over long-term cardiovascular risk:** cardiovascular deaths were more common (albeit not statistically significantly) in safety studies comparing febuxostat to allopurinol 300 mg, and therefore it s not recommended in patients with ischaemic heart disease or heart failure. Unfortunately, this encompasses a reasonable number of patients with renal disease and secondary gout.

As with allopurinol, there is drug interaction with azathioprine.
Benzbromarone

Uricosuric drugs such as sulfinpyrazone and probenecid are less efficient at lowering SUA than xanthine oxidase inhibitors and are contraindicated in patients with significant renal impairment due to: (1) even less efficacy, but also (2) the risk of worsening renal impairment through intra-tubular deposition of uric acid crystals. However, benzbromarone is a uricosuric, which is very efficient at lowering SUA, and which is still effective in patients with mild-moderate impairment (e.g. plasma creatinine up to 500 μmol/l). It is started at 50 mg/day and can be titrated up at monthly increments of 50 mg until the therapeutic target or the top dose of 200 mg is reached. It has restricted availability because of reports, largely confined to Asia, of hepatotoxicity, which is rarely fatal. Nevertheless, it is available on a named patient basis and can be a useful drug in some patients. Regular liver function checks are recommended with each dose increment and then 3 monthly for maintenance.

Other treatments that have a mild uricosuric and ULT effect (up to 20–25% of SUA) are losartan, clofibrate and vitamin C. Although losartan and clofibrate are insufficient as ULT on their own, it makes sense to use them when a lipid-lowering agent or anti-hypertensive is required in a patient with gout and renal disease. However, whether they have efficacy in patients with renal impairment is unknown.

Uricase

In the Eocene era, man, along with other mammals and many birds and reptiles, lost the ability to produce the enzyme uricase. However, this enzyme can be given parenterally and can cause dramatic reductions in SUA to close to zero. Rasburicase (recombinant uricase from Aspergillus favus) is licensed for use in prophylaxis of tumour lysis syndrome, but it is highly immunogenic and unsuitable for repeated administration. However, a recombinant polyethylene glycol-conjugated mammalian uricase (Pegloticase) has been developed, which may be less immunogenic. Limited trials of repeat intravenous infusion of this product for c. 3 months in patients with treatment-failure gout, including patients with renal disease, have shown regular marked lowering of SUA and rapid reduction in tophus size in some patients, but a high incidence of severe flares of gout, a high drop-out rate (one-third) and development of antibodies to the compound in three-quarters of patients. Therefore at present, the benefits of such salvage treatment for treatment failure patients remains unclear.

Summary

Gout is common in patients with renal impairment and treatment must be individualized according to the level of renal impairment. Intra-articular corticosteroid injection is an excellent option for acute mono-articular attacks of gout. The use of febuxostat is likely to be a major advance in ULT in renal patients.

Take home points

1. Gout is common, and increasing in prevalence in part due to the increasing frequency of end-stage renal disease.
2. Renal disease can cause chronic gross elevation of SUA above the saturation point for MSU crystal formation – the prerequisite for gout.

3. Other risk factors for gout include genetic predisposition, age, male gender, obesity, diet/lifestyle and OA.

4. Renal disease often associates with atypical clinical presentations of gout and difficulties in management due to increased toxicity or contraindication of drugs that are recommended.

5. Education, information access and lifestyle advice are important in patients with renal disease and gout.

6. In patients with renal disease, the acute mono-articular attack is best managed by local ice-packs together with aspiration and injection of intra-articular corticosteroid – this also allows confirmation of the diagnosis.

7. Polyarticular attacks of gout in renal patients can be treated with a short course of systemic corticosteroids.

8. The aim of lifestyle advice and ULT is to reduce the SUA below the saturation point for MSU crystal formation – the therapeutic target is to bring the SUA well below 360 μmol/l (6 mg/dl).

9. Allopurinol can be used at adjusted, lower doses in patients with renal disease but the therapeutic target may not always be reached.

10. Febuxostat is a new alternative to consider for patients with renal disease who are intolerant of, or unsuitable for, allopurinol.

11. NSAIDs, colchicine, sulphinpyrazone and probenecid are contraindicated in patients with severe renal disease; however, the uricosuric benz bromarone can be an effective ULT in patients with mild-moderate renal impairment.

12. Biological therapies that block IL-1β have been shown to be very effective in the treatment of acute attacks and may reduce the frequency of acute gout.

References

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest

* Recent review demonstrating the increasing prevalence of gout.


** Approximately 75% of patients with gout in hospital setting have renal impairment.
* Many of the drugs used for gout are contraindicated in patients with renal failure.

** European evidence-based guidelines for the management of gout.

** UK evidence-based guidelines for the management of gout.


* Update on risk factors and improved understanding of pathophysiology of gout.


* Important advance in the understanding of renal urate handling.

* Important advance in the understanding of renal urate handling.


* Vitamin C has urate lowering effects.


**Diuretic use is an important risk factor for gout.**


*The presence of osteoarthritis explains why joints such as the 1st MTPJ are susceptible to gout attacks.*


**European evidence-based recommendations for making the diagnosis of gout.**


*Gout can be confirmed by synovial fluid analysis between attacks.*


**Pathophysiological explanation of the inflammatory process triggered by uric acid crystals.**


* A potential new agent for acute gout, which could be used in patients with renal failure.


* Allopurinol toxicity is a significant concern in patients with renal impairment.


** Feboxostat is an important option for urate lowering therapy in gout patients with renal impairment.


* Losartan and fenofibrate have modest urate lowering effects.


Introduction
The earliest cases of nephrogenic systemic fibrosis (NSF) were recognized in 1997.\(^1\) Cowper et al. described 15 patients with renal failure who developed a scleroderma-like fibrosing disorder, which they termed a ‘scleromyxedema-like disorder of renal-dialysis patients’.\(^1\) The distinct clinical and histopathological findings were further elucidated in 2001 by the same authors, who then coined the term ‘nephrogenic fibrosing dermatomyopathy’ to reflect the obvious dermatological changes found in the presence of advanced kidney disease.\(^2\) It subsequently became evident that the disease also had systemic features with involvement of the pleura, pericardium, lungs, joints and striated muscle (including diaphragm and myocardium).\(^3,4\) To account for these observed systemic manifestations that often characterize this disease, the name was later changed to the currently accepted term of nephrogenic systemic fibrosis (NSF).\(^5\)

Pathophysiology
The cause of NSF remained unclear until 2006, when Grobner first suggested that an association existed between NSF and gadolinium-based contrast (GBC) exposure.\(^6\) This relationship has since been confirmed in several studies.\(^7–12\) The current and most widely accepted theory on the pathogenesis of NSF needs to be understood in the context of GBC pharmacological properties. Gadolinium in its unbound ionic form (Gd\(^{3+}\)) is highly toxic and therefore sequestered by a non-toxic organic molecule or chelator.\(^13,14\) Dissociation of Gd\(^{3+}\) from the chelate may occur through a process called transmetallation, in which the chelator binds to some other endogenous metal such as zinc or copper, thereby releasing Gd\(^{3+}\); it is this free gadolinium that appears to trigger a cascade of events that ultimately lead to the development of NSF.\(^15\) Importantly, as discussed below, it is the prolonged blood half-life of GBC in the context of advanced renal failure that permits transmetallation to take place.

GBC chelates can be categorized based on their biochemical structure and charge (see Table 31.1). Macrocyclic chelates bind Gd\(^{3+}\) more tightly than linear chelates, thus possessing greater stability and lower dissociation rates.\(^16\) Individual stability constants (thermodynamic, conditional, and kinetic) for each GBC agent characterize its ability to bind gadolinium ion and prevent release of toxic free gadolinium.\(^17\) Such stability constants vary substantially, with gadodiamide and gadoversetamide possessing values

* Conflict of interest: Dr. Fine has been retained in legal consultation involving gadolinium and NSF
that are lower by $100$- to $1000$-fold compared with gadobenate and gadoteridol.

When assessing kinetic stability, a measurement of how long it takes for a GBC agent to release Gd$^{3+}$, it becomes clear that gadodiamide and gadopentetate are significantly less stable than their macrocyclic counterpart gadoteridol. Thus, it is not surprising that the lower the overall stability of a GBC agent, the greater the risk of transmetallation and therefore toxicity.

It has been postulated that, once dissociated, Gd$^{3+}$ deposits into skin and other organs setting off a series of poorly understood events that eventually result in oedema and fibrosis. Recent findings of gadolinium deposition in the skin of patients with NSF using scanning electron microscopy and energy dispersive x-ray spectroscopy support this hypothesis. High et al. provided further evidence when they quantified tissue Gd$^{3+}$ in those with NSF and found 35- to 150-fold higher content than in healthy individuals exposed to GBC. More recent studies suggest that the gadolinium identified on biopsy is in its free form, further supporting the proposed mechanism of transmetallation. Moreover, it appears that vascular trauma, endothelial dysfunction

<table>
<thead>
<tr>
<th>GBC* formulation</th>
<th>Year of introduction</th>
<th>Charge</th>
<th>Molecular structure</th>
<th>Probable risk of NSF †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate (Magnevist)</td>
<td>1988</td>
<td>Ionic</td>
<td>Linear</td>
<td>Medium</td>
</tr>
<tr>
<td>Gadoteridol (Prohance)</td>
<td>1992</td>
<td>Non-ionic</td>
<td>Cyclic</td>
<td>Very low</td>
</tr>
<tr>
<td>Gadodiamide (Omniscan)</td>
<td>1993</td>
<td>Non-ionic</td>
<td>Linear</td>
<td>High</td>
</tr>
<tr>
<td>Gadoversetamide (OptiMARK)</td>
<td>1999</td>
<td>Non-ionic</td>
<td>Linear</td>
<td>Medium</td>
</tr>
<tr>
<td>Gadobenate (MultiHance)</td>
<td>1997</td>
<td>Ionic</td>
<td>Linear</td>
<td>Low</td>
</tr>
<tr>
<td>Gadofosveset (Vasovist)</td>
<td>2006</td>
<td>Ionic</td>
<td>Linear</td>
<td>Unknown</td>
</tr>
<tr>
<td>Gadoxetate (Primovist)</td>
<td>2006</td>
<td>Ionic</td>
<td>Linear</td>
<td>Unknown</td>
</tr>
<tr>
<td>Gadoterate‡ (Dotarem)</td>
<td>1989</td>
<td>Ionic</td>
<td>Cyclic</td>
<td>Very low</td>
</tr>
<tr>
<td>Gadobutrol‡ (Gadovist)</td>
<td>2003</td>
<td>Non-ionic</td>
<td>Cyclic</td>
<td>Very low</td>
</tr>
</tbody>
</table>

* GBC: Gadolinium-based contrast.
† Opinion and table based on summation of several references. High et al. provided further evidence when they quantified tissue Gd$^{3+}$ in those with NSF and found 35- to 150-fold higher content than in healthy individuals exposed to GBC. More recent studies suggest that the gadolinium identified on biopsy is in its free form, further supporting the proposed mechanism of transmetallation. Moreover, it appears that vascular trauma, endothelial dysfunction
and/or transudation (oedema) allows Gd$^{3+}$ to enter tissues more readily. This may explain the preponderance of initial symptoms in dependent areas of the limbs.

It is likely to be the prolonged half-life of GBC in the context of renal failure that predisposes to the transmetallation and dissociation of Gd$^{3+}$ from its chelate. Following intravenous injection, GBC is excreted unchanged by the kidneys via glomerular filtration in a patient with normal renal function. However, the elimination half-life, which is approximately 1.6 hours in normal individuals, is increased approximately 4- to 33-fold in renal insufficiency, depending on the level of GFR. This prolonged time in the body increases the potential for Gd$^{3+}$ transmetallation, tissue exposure and thus deposition. It should be noted that there are a small number of cases of NSF described where no exposure to gadolinium was found, suggesting the possibility of other triggers.

Interestingly, in a report by Deng et al., the skin of three patients with NSF but no apparent history of GBC exposure was examined. All three patients had gadolinium present in their skin biopsies.

**Clinical presentation**

As suggested by its former name, nephrogenic fibrosing dermopathy, the cardinal feature of this disorder is skin involvement. Symptoms can begin within 2 days of exposure, with most occurring by 2 months. More distant exposures have also been described. Initial signs and symptoms may include tightening and burning of the skin, often associated with erythema and oedema, as well as sharp and sometimes excruciating pain. Involvement tends to be symmetrical, with a predilection for the extremities more so than the trunk, and generally sparing of the face. The dependent lower extremities are more severely involved than the upper extremities. Dermal induration may occur in the form of plaques, nodules and/or papules resulting in a ‘woody’ texture on palpation. A *peau d’orange* or ‘cobblestoning’ appearance may also be present. These findings often progress over weeks to months with extensive dermal fibrosis involving entire limbs. Ultimately, the patient may develop severe joint contractures and marked limitations in mobility, often resulting in wheelchair dependence.

A fulminant presentation is seen in approximately 5% of patients who develop a rapidly progressive course over as short a time as 2 weeks. Systemic organ involvement, including fibrosis of the heart, lungs, diaphragm, skeletal muscle and other organs, has been reported and associated with fatal outcomes.

**Epidemiology**

Although most frequent in those with end-stage renal disease (ESRD), NSF has been seen in those with stage 4 and 5 chronic kidney disease (CKD) as well as acute kidney injury (AKI). Incidence rates have been difficult to calculate due to lack of exposure data in most studies. However, one small case-control study did find 4.3 cases of NSF per 1000 patient-years among haemodialysis patients, with an absolute risk of 3.4% in the exposed patient. It is notable that incidence rates in a Centers for Disease Control study of 19 NSF patients were much higher in peritoneal dialysis (4.6 cases/100 patients) than for haemodialysis (0.61 cases/100 patients). This is likely to be related to the difference in GBC clearance achieved by these two dialysis modalities.
NSF has no predilection for gender, race, nationality or age group. Those with liver disease, lower body weight or lower muscle mass appear to be at greater risk, as GFR is often overestimated in these subsets of patients. Risk is also likely to be increased by multiple exposures to GBC in close proximity. Related host co-factors have not yet been identified, although elevated serum calcium and phosphate concentrations, exposure to high-dose erythropoietin and iron overload have been considered.31,32

Diagnosis

The diagnosis of NSF requires not only hallmark clinical manifestations but also corresponding histopathology. Suspicious clinical findings in a patient with underlying kidney disease (AKI, CKD stages 4 and 5) who has been exposed to a GBC agent should prompt a skin biopsy. An incisional or deep punch biopsy to allow examination of the dermis, epidermis and subcutaneous fat is required. The primary feature is the presence of collagen bundles with increased dermal spindle cells that stain for CD34 and procollagen I.33,34 Factor XIIIA positive and CD-68 positive multi-nucleated cells may also be identified. Early on, mucin and elastic fibres are often noted, the latter of which is usually present in significant numbers. Importantly, an inflammatory infiltrate is absent, distinguishing this from fasciitis and other inflammatory skin disorders.33,34

The major differential diagnosis includes scleroderma, eosinophilic fasciitis, morphea, scleromyxedema and calcific uremic arteriolopathy. Scleroderma is characterized by facial and truncal involvement, sclerodactyly and Raynaud’s phenomenon (in addition to other systemic features) with skin histology demonstrating normal or decreased numbers of fibroblasts despite an increase in activity. Scleromyxedema may also involve the face and trunk, but is classically associated with a paraproteinemia on laboratory testing. Calcific uremic arteriolopathy (also known as calciphylaxis) also occurs in those with kidney failure but is distinguished clinically by focal areas of cutaneous necrosis, ulceration and livedo reticularis; skin biopsy often reveals medial calcification of the vasculature with intimal fibrosis and luminal thrombosis. Eosinophilic fasciitis is differentiated by a peripheral blood eosinophilia.35

Prevention of NSF

As NSF can be a particularly devastating disease with few treatment options (see below), the most important intervention is prevention. Strategies to do so are multi-pronged and have been successful in dramatically reducing the incidence of this disease.36

Avoidance of GBC exposure in at-risk patients

GBC agents are contraindicated in those with ESRD, CKD with estimated glomerular filtration rate (GFR) <30 ml/min/1.73m² (stages 4 and 5) and AKI. It has become common practice to use the 4-variable MDRD formula in estimating GFR.37 Importantly, no estimating formula can be used in the context of a rising serum creatinine concentration as occurs with AKI. If a patient has AKI, one must assume a GFR <15 ml/min/1.73m² unless proven otherwise.
In those with low muscle mass, the MDRD estimated GFR may overestimate the true GFR. Therefore, the Cockcroft-Gault equation or a 24 hour urine-based creatinine clearance may be useful in such patients.

**Selection of the lowest risk GBC agent**

When GBC use is deemed necessary in the high-risk individual, an agent comprising a macrocyclic chelate (gadoteridol in the USA, gadoterate in Europe) is recommended. No published cases of NSF have been described with singular use of gadoteridol. In addition, a retrospective study demonstrated no cases of NSF in haemodialysis patients exposed to gadoteridol at a single institution over a 7-year period. This is not unexpected given the pharmacological properties of this particular GBC agent.

Gadodiamide (linear and non-ionic) appears to have the greatest risk for NSF, as the majority of cases reported to the FDA thus far have been associated with this particular agent. The significant preponderance of this agent in such cases is unlikely to be related to market share, reporting bias or publication bias. In fact, gadopentetate (linear and ionic) had the greatest market share during this time and was responsible for approximately a quarter of all cases reported to the FDA. Based on the available data, gadodiamide, gadopentetate and gadoversetamide should be avoided in high-risk patients. Instead, a macrocyclic agent like gadoteridol is a much safer alternative.

Some have also used gadobenate without incidence because its advantageous imaging qualities allow for lower doses compared with other approved GBC agents. To date, there have been no confirmed cases of NSF reported with an isolated exposure to gadobenate.

**Use of lower doses of GBC**

The use of higher ‘off-label’ doses of GBC agents (0.3–0.4 mmol/kg), which were utilized for non-invasive vascular studies, may have contributed to the emergence of NSF several years after these agents became available. In addition, repeated GBC agent exposure over a relatively short period of time appears to increase the risk for developing NSF. This is likely to be related to an accumulation of gadolinium between the multiple exposures. Nevertheless, there have also been some cases describing remote exposures to GBC agents leading to increased susceptibility for NSF on subsequent exposure to GBC. Thus, if an exposure is necessary, then the lowest possible dose should be used.

**Development of a protocol with radiology and nephrology departments**

As discussed previously, assessment of renal function prior to contrast administration is of utmost importance. Patients with ESRD, CKD with estimated GFR <30 ml/min/1.73m² (stages 4 and 5), and AKI should be identified using the 4-variable MDRD formula in estimating GFR with caveats as previously noted. As the MDRD is invalid in the setting of ESRD and AKI, these diagnoses should be determined through other means (i.e. the patient’s medical history) as part of the consent process for GBC administration. Once the most at-risk patients are identified, alternative radiological imaging modalities to
GBC-enhanced magnetic resonance imaging (MRI) should be utilized if possible. Newer MRI techniques without GBC enhancement (3D time-of-flight magnetic resonance angiography (MRA), phase-contrast angiography, and arterial spin labelling-MR) provide excellent information about blood vessels and blood flow.²³ In the future, MR imaging with ultra-small paramagnetic iron oxide particles may offer an alternative for those needing a contrast-based scan for diagnosis.²⁴ However, as contrast-enhanced MRI/MRA studies remain as extremely important imaging modalities, their use may be required in some high-risk individuals. In such circumstances, a macrocyclic chelate employed at the lowest possible dose is recommended. Both a radiologist and a nephrologist should be consulted in these instances.

At our own institution, a protocol based on the prevention principles described above was put in place by January 2007 as a collaborative effort between the radiologists and nephrologists. This has resulted in the elimination of NSF at our hospital.²⁶

The role of haemodialysis

Although haemodialysis efficiently removes GBC that is present in plasma, its removal from the body is incomplete.²⁴ Furthermore, the catalytic insult may already have occurred by the time a haemodialysis treatment is started.⁴⁵ It should be recognized that GBC removal after one treatment averages 65–73.8%; after three to four sessions less than 1% of the agent remains in the plasma.²⁴,⁴⁶ Peritoneal dialysis, on the other hand, is an ineffective method of GBC removal (T₁/₂ of 52.7 hours).²⁴ Because not all of the Gd³⁺ is removed with haemodialysis, prolonged tissue exposure occurs, as is reflected by the development of NSF in patients despite having received consecutive haemodialysis treatments following GBC exposure.⁸ Therefore, avoidance of GBC is necessary in all patients with advanced kidney disease (GFR <30 ml/min/1.73m²), regardless of the availability of haemodialysis.⁴⁵,⁴⁷,⁴⁸ In other words, the ability to perform haemodialysis after GBC exposure does not justify GBC use. However, if the need for GBC is deemed vital, then immediate haemodialysis should be instituted in those with ESRD after exposure, with repeated treatments on consecutive days.

Treatment

Unfortunately, there is a lack of universally effective therapy once NSF develops. Several interventions have been described, primarily in anecdotal case reports and very small case series. They are as listed in Table 31.2.

Physical and occupational therapy is the mainstay of treatment for NSF. More specifically, these interventions are essential in helping to prevent or slow the progression of joint contractures. Adequate pain relief, often with narcotics, is necessary for patient comfort and tolerance of physical therapy.⁴⁹

Other approaches have been used in only a small subset of patients and with variable success. Treatments with anecdotal benefit include extracorporeal photopheresis and infusions of sodium thiosulfate, another substance with chelating properties.⁴⁹ Recently, therapies with imatinib⁵⁰ and rapamycin⁵¹ have been described. Other immunosuppressive agents, topical medications and phototherapies have shown limited success.
Of note, AKI resolution has been observed to result in regression of lesions in some patients.\textsuperscript{2,6,52–54} It is presumed that recovery from AKI allows gadolinium and other profibrotic mediators to be cleared, although definitive evidence for this is not available. Based on these findings, it is not surprising that improvement following kidney transplantation has also been described.\textsuperscript{6,55} However, responses post transplant have not been consistent.\textsuperscript{56}

**Conclusion**

With the high and increasing rates of AKI, CKD and ESRD seen among hospitalized patients,\textsuperscript{57} the need for vigilance when obtaining imaging with GBC agents becomes particularly important in the inpatient setting. As a preventable disease, it is our responsibility as physicians to fully understand the risk factors and potential pitfalls that may result in a patient exposed to these agents. Nephrologists, radiologists and primary care physicians alike must act as a firewall between the patient and the imaging study that may put him or her at risk for this devastating disorder.

The FDA has sent out several alerts since June 2006 regarding this issue, with the most recent one in May 2007.\textsuperscript{58–61} In its ‘Information for Healthcare Professionals’ alert, the FDA provided some guidance for the use of GBC agents in high-risk populations. These are included in our final recommendations shown in Table 31.3.\textsuperscript{61} Patients with chronic liver disease or recent liver transplant, with associated kidney insufficiency of any severity, have also been identified by the FDA as a risk group.\textsuperscript{62} Although the European Society of Urogenital Radiology and the American College of Radiology\textsuperscript{63} have established recommendations regarding safe use of GBC agents, nephrology

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**Table 31.2 Treatment possibilities in nephrogenic systemic fibrosis**

<table>
<thead>
<tr>
<th>Therapies most likely to benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney transplant (in ESRD)</td>
</tr>
<tr>
<td>Physical and occupational therapy</td>
</tr>
<tr>
<td>Pain control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapies with anecdotal success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracorporeal photopheresis</td>
</tr>
<tr>
<td>Sodium thiosulfate</td>
</tr>
<tr>
<td>Rapamycin</td>
</tr>
<tr>
<td>Imatinib</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapies with limited success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs—glucocorticoids, pentoxifylline, cyclophosphamide, thalidomide</td>
</tr>
<tr>
<td>Immunomodulatory—plasmapheresis, intravenous immunoglobulin</td>
</tr>
<tr>
<td>Local—intralesional IFN-α, topical calcipotriene, other phototherapies</td>
</tr>
</tbody>
</table>

* Adapted and expanded from Fine et al.\textsuperscript{47}

ESRD, end-stage renal disease; IFN, interferon.
Identification of GBC as a major culprit in the development of NSF, and hence avoidance of this agent in those at highest risk, is expected to reduce the incidence of NSF. It is likely that the future will bring forth a better understanding of the underlying mechanisms of gadolinium-induced NSF, and with this knowledge, safer strategies for GBC usage can be developed. Nevertheless, until safer contrast agents become available, avoidance of GBC exposure in those with advanced acute or chronic kidney disease remains our most important defence.

**Take home points**

1. NSF can be a devastating disorder resulting in excruciating pain and/or severe disability.
2. Gadolinium triggers NSF.
3. Not all GBC agents are created equal. Risk of NSF is dependent on the individual stability of each GBC agent.
4. The prolonged half-life of GBC agents in renal failure (GFR <30 ml/min/1.73m²) predisposes to NSF by allowing for dissociation of toxic free gadolinium.
5. The deposition of gadolinium in tissue triggers a cascade of events culminating in the clinical presentation of NSF.
6. Treatments for NSF are limited and still being investigated. Until then, our best defence against NSF is prevention.
7. For those with NSF, physical and occupational therapy are critical in maintaining functional status.
References

Papers of particular interest have been highlighted as:

* of special interest
** of outstanding interest


**Study demonstrating the presence of gadolinium in tissue of patients with NSF.**
**Demonstration of gadolinium deposition in skin in NSF patient.**
   *Review of the natural history and clinical presentation of NSF.
   *Retrospective study supporting the association between gadolinium exposure in NSF and the use of a hospital-wide policy aimed at prevention of NSF.
   *Retrospective study on haemodialysis dependent patients who did not develop NSF following exposure to gadoteridol.


*Case descriptions of patients who developed NSF following liver transplantation.*


*Review of the thermodynamic and kinetic properties of gadolinium-based agents and possible contribution to the development NSF.*
Chapter 32

Rheumatological complications of renal disease and transplantation

Sharmin Nizam, Zunaid Karim, and Paul Emery

Introduction

Renal disease and transplantation can present with diverse acute and chronic musculoskeletal problems affecting morbidity, with a third of all transplant patients affected. Predisposing factors include pre-existing osteodystrophy, persistent hyperparathyroidism, graft malfunction, obesity and post-transplant immunosuppression.

Transplantation-related problems

Renal osteodystrophy

Renal osteodystrophy encompasses a range of bone diseases including osteomalacia, secondary hyperparathyroidism, osteoporosis, aluminium toxicity and \( \beta_2 \) microglobulin disease.\(^1\) It is a multi-factorial disorder of bone remodelling secondary to renal insufficiency-induced imbalances in mineral homeostasis. Secondary hyperparathyroidism leads to bone resorption, whereas 1,25 dihydroxyvitamin D3 deficiency, due to inadequate hydroxylation of precursors, results in decreased intestinal absorption of calcium, further stimulating parathyroid hormone secretion.\(^1\)

Histologically, renal osteodystrophy is classified into osteitis fibrosa, osteomalacia or adynamic bone disease.\(^2\) Osteitis fibrosa, primarily due to secondary hyperparathyroidism comprises marrow fibrosis, bone resorption and subperiosteal erosions. Affected sites include the phalanges and proximal femur, tibia and humerus.\(^3\) Osteomalacia is characterized by defective mineralization of trabecular and cortical bone.\(^2,\)\(^3\) Adynamic bone disease (ABD), seen in end-stage renal disease without secondary hyperparathyroidism, is characterized by low bone resorption and formation with normal or low amounts of osteoid tissue.\(^2\) Postulated causes include hypogonadism and direct suppression of bone remodelling or deficiency of a factor involved in bone formation or growth.\(^2\) Adynamic bone leads to an increased risk of fractures. Age, duration of dialysis, female sex and diabetes add to the risk of ABD.\(^4,\)\(^5\) Inadequate uptake by bone leaves other tissues vulnerable to calcium deposition (metastatic calcification).\(^3\) Commonly affected areas are medium sized blood vessels, peri-articular soft tissues (tumoral calcinosis), heart, lung and kidney.

Most patients undergoing a renal transplant have pre-existing osteodystrophy and osteopaenia.\(^5,\)\(^6,\)\(^7\) Post transplant, parathormone (PTH) levels initially fall rapidly
followed by a slower decline with most stabilizing within a year. Persistent elevations are associated with a longer duration of dialysis pre-transplant, but PTH levels do not necessarily correlate with bone disease. Metabolic acidosis and hypophosphataemia post transplant increase the risk of osteoporosis and osteomalacia respectively. Mutations in the gene for phosphatonin, a hormonal PTH regulator, are another recognized cause of osteomalacia.

**Clinical features of renal osteodystrophy**

Patients may present with bone pain, slow healing fractures or waddling gait due to proximal weakness.

**Diagnosis of renal osteodystrophy**

**Serum markers**

Serum alkaline phosphatase, calcium and parathyroid hormone measurements can be used to evaluate osteodystrophy. Secondary hyperparathyroidism is typically linked with high levels of alkaline phosphatase and PTH levels. Low PTH levels strongly suggest the presence of adynamic bone, although not exclusively. Aluminium-induced bone disease often results in lower alkaline phosphatase levels and less than twice normal PTH levels. Serum osteocalcin, secreted by osteoblasts, can act as a confirmatory biochemical marker of renal osteodystrophy as it correlates with PTH and alkaline phosphatase before and after transplant. Cyclosporine and prednisolone can stimulate increased levels of alkaline phosphatase (ALP) making this an unreliable marker of bone resorption.

**Imaging and histology**

Radiological abnormalities often appear late in disease. Plain radiographs and bone scans may show fractures, whereas magnetic resonance imaging (MRI) may reveal intramedullary extensions of fracture lines. The diagnostic gold standard is a bone biopsy.

**Management of renal osteodystrophy**

Treatment depends on the underlying cause. Analgesics, maintenance of serum calcium and phosphate levels, vitamin D replacement therapy, phosphate binders and reduced exposure to aluminium may help. In ABD, treatment should be aimed at increasing plasma levels of intact PTH to increase bone turnover. In some cases, renal transplantation may lead to improvements in bone metabolism, although an effect on ABD is unclear. Refractory tertiary hyperparathyroidism may require parathyroidectomy. The optimal timing of parathyroid surgery is debatable. Some groups recommend waiting at least 1 year post transplant to allow for possible resolution of hyperparathyroidism. Cinacalcet, a calcimimetic agent, is an alternative treatment option in refractory secondary hyperparathyroidism in patients with uncontrolled levels of PTH (>85 pmol/l or 800 pg/ml), provided calcium levels are not low. Dosage is titrated gradually to achieve a target PTH level between 15.9 and 31.8 pmol/l (150–300 pg/ml).
Osteopaenia/osteoporosis and fractures (Table 32.1)

Osteopaenia is common post transplant due to pre-transplant bone disease, steroid therapy and hyperparathyroidism. The latter may persist up to 2 years post transplant in 25–50% of recipients. These factors contribute to rapid reductions in bone mass post transplant, and this is worse in the first 6 months. Fracture risk is higher in kidney transplant recipients compared with dialysis patients, and four times higher than the general population. However, the exact degree of correlation between bone mass (as measured by bone mass densitometry (BMD)) and fracture frequency is uncertain. Proximal weakness due to osteomalacia and minimal weightbearing activities pre and post transplant may contribute to falls and increase the fracture risk. Therapeutic use of glucocorticoids, immunosuppressive therapy, female gender, post menopausal status, persistent uraemia and hyperparathyroidism are additional risk factors for osteopaenia.

Genetic factors have also been implicated in improvement of bone density following renal transplant, with patients homozygous recessive for vitamin D receptor genes being shown to recover more bone in the first year post transplant compared with heterozygous or homozygous dominant patients.

Effect of immunosuppression

Prednisolone dosage is one of the most important risk factors for bone loss. Glucocorticoids inhibit bone formation and intestinal absorption of calcium while

Table 32.1 Risk factors for renal osteodystrophy/osteoporosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary hyperparathyroidism</td>
<td>↑ bone resorption</td>
</tr>
<tr>
<td></td>
<td>↓ intestinal calcium absorption</td>
</tr>
<tr>
<td>hypogonadism</td>
<td></td>
</tr>
<tr>
<td>↑ age</td>
<td></td>
</tr>
<tr>
<td>↑ dialysis duration</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Persistent uraemia post transplant</td>
<td></td>
</tr>
<tr>
<td>Metabolic acidosis post transplant</td>
<td></td>
</tr>
<tr>
<td>↑ glucocorticoid use</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressant therapy (debatable link)</td>
<td>Cyclosporine and tacrolimus linked to higher bone turnover and resorption through nephrotoxic effects</td>
</tr>
<tr>
<td></td>
<td>? decreased gonadotrophin synthesis</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>↑ urinary calcium excretion</td>
</tr>
<tr>
<td>Mutations in phosphatonin gene</td>
<td></td>
</tr>
</tbody>
</table>
promoting bone resorption.\textsuperscript{19} Direct tubular action of glucocorticoids promotes calciuria, exacerbating secondary hyperparathyroidism. Glucocorticoids also suppress gonadotrophin secretion and indirectly inhibit growth hormone secretion leading to reduced bioavailability of skeletal growth factors and myopathy (Table 32.2).

Renal allograft recipients receive immunosuppressants including cyclosporine, tacrolimus, azathioprine or mycophenolate mofetil. Cyclosporine and tacrolimus are thought to increase bone turnover and resorption, and to decrease gonadal steroid synthesis.\textsuperscript{4,19} The effect of cyclosporine, which increases osteocalcin levels, may be additive to the low-turnover osteodystrophy produced by glucocorticoids. The nephrotoxic effects of cyclosporine and tacrolimus can lead to secondary hyperparathyroidism when glomerular filtration rates drop to the range of 40–50\% expected.\textsuperscript{4} However, the actual effect of cyclosporine on BMD is difficult to interpret with confounding factors such as cumulative steroid dose and previous aluminium exposure. It has also been suggested that cyclosporine has a protective role\textsuperscript{4} possibly by reducing steroid dependence. A retrospective study found no difference in BMD scores in groups receiving cyclosporine plus prednisolone compared with azathioprine and prednisolone.\textsuperscript{24}

### Prevention, monitoring and management of osteoporosis

Table 32.3

<table>
<thead>
<tr>
<th>Site</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>↓ bone formation, ↑ bone resorption</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>↓ calcium absorption</td>
</tr>
<tr>
<td>Kidney</td>
<td>↑ urinary calcium loss</td>
</tr>
<tr>
<td>Muscle</td>
<td>Myopathy (increases risk of falls and fractures)</td>
</tr>
<tr>
<td>Hypothalamic–pituitary axis</td>
<td>↓ growth hormone and gonadotrophin secretion</td>
</tr>
<tr>
<td></td>
<td>↓ bioavailability of skeletal growth factors</td>
</tr>
<tr>
<td></td>
<td>↓ ovarian/testicular function</td>
</tr>
</tbody>
</table>

Immunosuppressive therapy should be optimized to reduce glucocorticoid dependence. The value of bone mineral densitometry (DEXA) measurements in renal disease and transplant patients is debatable but serial measurements, particularly at 1 and 2 years post transplant can still be useful.\textsuperscript{4,6} Plain radiographs are only indicated if there is suspicion of fracture.

If low BMD scores are noted peri and post transplant, bisphosphonates should be considered.\textsuperscript{5,6,19,22,25} A small, randomized study of transplant recipients treated in the early post-transplant period showed that control subjects lost 6.4\% of BMD at 12 months compared with no loss of BMD in the pamidronate group.\textsuperscript{26} Alendronate has been shown to progressively increase bone mass in the hip\textsuperscript{27} and in some studies, spine.\textsuperscript{4} The benefit of etidronate is controversial, but intermittent administration is suggested.\textsuperscript{4} Calcitonin, an osteoclastic inhibitor may also be considered.\textsuperscript{4} Thiazides may counteract
OSTEONECROSIS

the negative effect of steroids on bone, albeit at risk of exacerbating other steroid complications (e.g. hyperlipidaemia). Furosemide can promote bone resorption via calciuria. If hypogonadism persists post transplant, hormone replacement therapy may be considered.

Osteonecrosis

The development of osteonecrosis (focal bone infarcts) after renal transplantation is well recognized although the reported incidence has reduced from 20% to 4% since the introduction of steroid-sparing agents like cyclosporine. Any site may be affected, although osteonecrosis or avascular necrosis (AVN) of the hip is most commonly found after renal transplantation. Cumulative steroid intake, post-transplant weight gain and prolonged dialysis period (not mode) are risk factors for osteonecrosis. Graft rejection increases the risk due to increased steroid requirements. Average weight gain at 1 year post transplant is approximately 10%, and is a predictive risk factor for AVN independent of steroid usage. Demographic factors such as female gender and black ethnicity have been linked directly to this, whereas advancing age appears to be inversely correlated.

Post-transplant hip pain can be due to gluteal tendon abnormalities. The pathogenesis is unclear but probably secondary to a combination of factors such as steroids, dialysis-related arthropathy, mechanical stress (from altered gait) and inflammatory enthesopathy. Transient, self-limiting knee pain with bone marrow oedema on MRI is also recognised.

Clinical features

Initially patients may be asymptomatic. However, with progressive joint damage and collapse, they may develop severe joint pain with limping and limitation of movement.

Table 32.3 Recommendations for prevention and management of osteoporosis

- Treat underlying disorders affecting bone and mineral metabolism
- Optimize immunosuppressive therapy as rapidly as possible and avoid/minimize dependence on glucocorticoids
- Resume weightbearing exercise as soon as possible
- Maintain adequate dietary calcium (1000 mg daily for men, 1500 mg daily for postmenopausal women)
- Adequate vitamin D (800 IU daily)
- Minimize lifestyle risk factors (avoid smoking, limit alcohol intake)
- Avoid loop diuretics
- Monitor BMD regularly and consider bisphosphonates or calcitonin
- Monitor gonadal hormone levels and consider hormonal replacement therapy if deficiencies noted

BMD, bone mass densitometry.
Diagnosis

Plain radiographs are often normal thus unhelpful in the initial stages. In the later stages, a subchondral crescent sign may appear followed by evidence of advanced degenerative changes, flattening of the articular surface and collapse of joint space. Bone scans may demonstrate photopaenic areas but MRI is more sensitive and specific in the early stages. If MRI findings are negative, bone SPECT (spectrum emission computerized tomography) is reported to be more sensitive (100%) post transplant. Radiological evidence should be evaluated in combination with the clinical context to make a definitive diagnosis.

Prevention and management

Limiting steroid use and treating pre-transplant osteodystrophy early plus bisphosphonate usage, reduces the risk of subsequent osteonecrosis. Immunosuppressants (e.g. cyclosporine and tacrolimus) can offer protection through reducing steroid requirement and rejection episodes post transplant. Hyperlipidaemia, secondary to steroids, can promote ischaemia of the femoral head suggesting a potential prophylactic role for statins. Management is mainly symptomatic (rest, analgesics). Surgical intervention (arthroplasty, core decompression) may need to be considered. Hemi-surface replacement of the femoral head is a newer technique best considered before significant joint destruction and collapse occurs.

Acute bone pain syndrome and reflex sympathetic dystrophy (RSD)

Acute bone pain syndrome or calcineurin-inhibitor induced pain syndrome (CIPS) is a rare debilitating condition affecting about 5% of solid organ, and between 19% and 27% of renal transplant patients. There is considerable overlap in features with RSD also recognized post transplant in association with immunosuppression such as cyclosporine and tacrolimus.

Clinical features

Patients usually present with symmetrical lower limb pain within a few months of starting immunosuppression with sparing of hips and spine. Pain is worse on weight-bearing, alleviated by rest and may require opiate analgesia. Additional findings in RSD include vasomotor instability and trophic ulceration. Polyneuropathy may occur.

Diagnosis and management

Clinical examination, inflammatory markers, serum cyclosporine or tacrolimus levels, and plain radiographs are usually normal. Bone scintigraphy may show increased tracer uptake in affected areas, whereas MRI shows patchy oedema in the bone and peri-articular soft tissue. There is no current proven treatment but the condition may resolve spontaneously over a period of months with no sequelae. Non-steroidal anti-inflammatory drugs (NSAIDs), calcium antagonists, clodronate and calcitonin may provide benefit.
Corticosteroids may offer prophylaxis against development of a full RSD pattern, although this is not proven.

**Acute hot joint**

An acute hot joint in transplant patients can be a diagnostic and therapeutic problem. Although differential diagnoses, as discussed below, should be considered, it should be noted that painful joint effusions can occur during periods of acute rejection, which resolve following treatment of the rejection (Table 32.4).

**Clinical features**

Patients may present with acute pain, swelling and limitation of movement of affected joints. There may be systemic symptoms of fever and rashes. Detailed history and examination of the patient can provide diagnostic clues but aspiration and synovial

---

**Table 32.4 Acute hot joint: features to aid diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>Sepsis</th>
<th>Gout</th>
<th>CPPD</th>
<th>Hydroxyapatite</th>
<th>Ca oxalate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synovial fluid</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appearance</td>
<td>Usually cloudy/turbid</td>
<td>Clear/turbid</td>
<td>Clear/</td>
<td></td>
<td>Similar to CPPD</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>Reduced</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WCC/ml</strong></td>
<td>&gt;25000</td>
<td>10000–20000</td>
<td>10,000–50,000</td>
<td>May be &gt;2000</td>
<td>May be &gt;2000</td>
</tr>
<tr>
<td><strong>Neutrophils</strong></td>
<td>∼95%</td>
<td>∼80%</td>
<td>∼80–90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Crystal examination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(light microscopy with polarized light)</td>
<td>Monosodium urate</td>
<td>Pyrophosphate</td>
<td>Basic calcium phosphate</td>
<td>Calcium oxalate</td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Needle</td>
<td>Rhomboid shape</td>
<td>Coin-like/irregular</td>
<td>Envelope/bipyramidal</td>
<td></td>
</tr>
<tr>
<td>Shape</td>
<td>Strong, negative</td>
<td>Weak, positive</td>
<td>Not birefringent (need electron microscopy to identify)</td>
<td>Irregular</td>
<td>Weak/strong</td>
</tr>
<tr>
<td>Birefringence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td>May see marked destruction over time</td>
<td>May show erosions</td>
<td>Chondrocalcinosis Often degenerative</td>
<td>Calcinic tendonitis</td>
<td>Like CPPD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Destructive arthropathic changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Occasional crystals visible as cloud-like opacities</td>
<td></td>
</tr>
</tbody>
</table>

*Aspiration of synovial fluid should be attempted to aid diagnosis and sent for gram stain, crystal examination and culture.

CPPD, calcium pyrophosphate deposition; WCC, white cell count.
fluid analysis should be considered where possible to aid appropriate management. Plain radiographs may occasionally be useful, for example chondrocalcinosis.

**Differential diagnoses for acute hot joint**

**Sepsis**

This tends to be mono- rather than polyarticular with significant pain, erythema and warmth of affected joints and systemic features (temperature, rigors). Renal transplant patients are particularly at risk due to impaired host defences as a consequence of renal impairment, immunosuppression and pre-existing joint damage.\(^38\) Due to immunosuppression, systemic features such as rigors may be masked. The frequency of septic arthritis has been reported at 1%, although the risk rises to 19% in those undergoing joint replacement after an organ transplant.\(^39\),\(^40\) A history of intra-articular corticosteroid injection, or previous infection should raise the index of suspicion. Gram-negative infections in this group have been associated with urinary tract infections,\(^41\) although opportunistic organisms such as mycobacteria and fungi,\(^42\) as well as common pathogens, all need to be considered.

**Management**

**Acute**

Joint aspiration is important in identifying the presence of infection and causative organism to guide appropriate antimicrobial therapy,\(^43\) and is also of therapeutic benefit. Needle aspiration is often adequate, although open incision and drainage may be required in cases of reaccumulation and persistence.

Empirical broad spectrum antibiotics therapy with anti-fungal cover, if required, is ideally commenced post aspiration but should not be delayed for this.

**Chronic**

Minimizing risk factors for infection is advised. In recurrent cases, prophylactic antimicrobial therapy may be warranted, although this must be weighed up against the risk of organisms developing resistance. Potential sites of infection must be reviewed and removal of prosthetic material may be required.

**Gout**

This is more common in renal insufficiency than renal failure, and is unusual in dialysis patients. Renal allograft recipients can develop a first attack of gout at any time from months to years post transplant.\(^44\) Interestingly, although hyperuricaemia is common in paediatric transplant patients, gout is rare.\(^45\)

Post-transplant gout has a reported prevalence of 2–13%. Persistent reduced creatinine clearance and cyclosporine or tacrolimus use are predisposing factors.\(^4\),\(^46\) Cyclosporine-related gout has an estimated incidence of 10% and may be due to cyclosporine causing tubular dysfunction leading to reduced uric acid excretion. Hypertension secondary to renal insufficiency or medication often necessitates use of diuretics, which can exacerbate hyperuricaemia.\(^4\),\(^46\) Tacrolimus has been associated with hyperuricaemia,
but there are reports of resistant gout improving following a switch from cyclosporine to tacrolimus.  

**Diagnosis of gout**

Patients may present with mono or oligoarticular pain and swelling associated with warmth and erythema over affected joints. First metatarsophalangeal joints, wrists, knees and elbows are commonly affected sites in transplant patients. There may be associated fever or chills with occasional leucocytosis on blood films. The C-reactive protein (CRP) may be high but uric acid levels are not necessarily elevated during an acute attack. Tophi can occur in transplant patients due to uric acid retention secondary to immunosuppression (cyclosporine and tacrolimus). Synovial fluid analysis typically shows negatively birefringent needle shaped crystals of monosodium urate.

**Management of gout**

**Acute**

Aspiration of joint fluid can be of diagnostic and therapeutic benefit. Short-term oral or intra-articular steroids can be useful. Colchicine and NSAIDs can help, although the latter is often avoided in transplant patients due to potential nephrotoxicity.

**Prophylactic and long term**

Dietary modifications (reduced alcohol, low purine intake) are advised. Amlodipine and losartan are useful alternatives to loop and thiazide diuretics as they have an additional benefit of lowering serum urate. Colchicine may be used prophylactically, but myotoxicity (reversible) is of concern in renal impairment or when used concomitantly with cyclosporine. Allopurinol should not be used in patients on azathioprine due to the risk of myelosuppression.

Uricosurics (e.g. probenecid) are unlikely to be effective in patients with significant graft dysfunction or renal impairment with the exception of benzbromarone, but patients should be monitored for hepatotoxicity. Febuxostat may be useful in patients with mild to moderate renal impairment. PEG-uricase and rasburicase are newer therapies aimed towards breaking down uric acid to allantoin to reduce hyperuricaemia. Clinical trials have been encouraging, although parenteral administration and possible development of anti-uricase antibodies may limit usage.

**CPPD arthropathy/pseudogout**

Calcium pyrophosphate deposition (CPPD) is not as common in renal disease as gout. It has been associated with Bartter’s syndrome. Acutely, it can present like gout with mono or oligoarticular joint inflammation, whereas in the chronic stages it resembles degenerative joint disease. Inflammation results from the deposition of crystals in the articular cartilage. Synovial fluid examination may reveal positively birefringent rhomboid crystals under polarized light. Predisposing factors include hyperparathyroidism, age, trauma, hypomagnesia, hypothyroidism, hypophosphatasia and haemochromatosis. However, treatment of the underlying condition may not alter the course of the arthritis.
Management of CPPD arthropathy/pseudogout

Acute
Radiographs may show chondrocalcinosis in affected joints, although it should be noted that rarely, infection may co-exist, so aspiration and synovial fluid analysis is advised. Intra-articular steroid injection of affected joints and non-steroidals are treatment options. Oral colchicine has been shown to be effective in prophylaxis but not in the treatment of acute disease.  

Hydroxyapatite-related arthropathy
Basic calcium phosphate crystals (BCP) in pathological tissues and fluid include carbonate-substituted apatite, octacalcium phosphate and tricalcium phosphate. Hyperphosphataemia in renal failure increases the risk of crystal deposition, which may be peri-articular (leading to acute episodes such as calcific rotator cuff or tendonitis) or intra-articular (causing more chronic, non-inflammatory degenerative changes). Milwaukee shoulder is an example of a rare but rapidly destructive arthropathy affecting the rotator cuff and glenohumeral joint caused by intra and/or peri-articular hydroxyapatite crystal deposition. Soft tissue or peri-articular deposition (tumoral calcinosis) can look like large clouds on plain films.

Management
In the acute setting colchicine or corticosteroids may help. The condition may prove resistant to treatment with recurrent episodes. If aspiration or intra-articular corticosteroid fails to help, arthroscopic calcium removal and bursectomy can be tried. Milwaukee shoulder is a difficult condition to manage with little benefit from steroids. Physiotherapy may be helpful. Prophylactic treatment is by dietary phosphate restriction, dialysis, use of phosphate binders and in resistant cases, parathyroidectomy.

Calcium oxalate deposition disease
Secondary oxalosis occurring in end-stage renal disease can lead to intra-articular and peri-articular deposition of calcium oxalate. Clinical manifestations resemble CPPD and gout with both acute and chronic joint inflammation. Tendon and soft tissue deposits have also been described.

Management
Treatment is similar to CPPD and gout with colchicines and/or corticosteroids.

Take home points
1. Both acute and chronic musculoskeletal problems can significantly affect morbidity of renal transplant patients
2. It is important to correct predisposing risk factors of renal osteodystrophy such as hyperparathyroidism
3. Aim for optimization of steroid-sparing immunosuppression to reduce risk of osteopaenia and osteonecrosis.

4. Joint aspiration should always be considered in the case of an acute hot joint.

5. Systemic features (fever, rigors) may be absent in septic joints in patients on immunosuppressants (e.g. post transplant).

6. Gout is more common in renal insufficiency than renal failure/dialysis patients and can occur any time post transplant (even years).

7. Avoid loop and thiazide diuretics if possible to reduce risk of gout.

References

Papers of particular interest have been highlighted as:
* of special interest
** of outstanding interest

   Comprehensive overview of joint problems seen in renal disease.

   Important review of pathogenesis of osteodystrophy.

   Useful overview of renal osteodystrophy.

   Reference guidelines for management of bone disease in renal patients.

   Important overview of causative factors and monitoring of transplant patients with bone disease.

   Of special interest for problems related to transplant patients.
   Important for information on renal osteodystrophy in transplant (7–16) (helped in summarizing topic).


   Useful reference for national guidelines to help with management. Useful for osteoporosis monitoring and management (*ref* 18–27) (*of special interest*).


REFERENCES

   Of interest as alternative causes for joint (hip) pain and radiological changes in transplant patients.
   Important references for summarizing aetiology and management of acute bone pain syndrome (35–37).
   Topical overview of unusual cause of pain in transplant population.
   Important for management of septic arthritis (38–43 * of special interest).
   Crystal arthropathy-related information summarized from 44–53.


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