SECTION 8

The patient with infections causing renal disease

CHAPTER 183

Malaria

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Overview

Malaria is widely prevalent in several tropical regions of the world including South and South East Asia, South and Central America, and sub-Saharan Africa. The humid and hot tropical climate supports multiplication of the disease vector, the *Anopheles* mosquito. According to the World Health Organization, about 3.3 billion people are at risk of malaria, 250 million develop the infection, and nearly 1 million die every year. There is a striking correlation between global distribution of malaria and poverty.

Four pathogenic species of malarial parasite, *Plasmodium vivax, Plasmodium ovale, Plasmodium malariae*, and *Plasmodium falciparum*, infect humans. Clinically significant renal dysfunction is mainly associated with *P. malariae* and *P. falciparum* infections. The former can cause a nephrotic syndrome due to immune complex-mediated glomerular disease, referred to as 'quartan malarial nephropathy'. The renal presentation in *P. falciparum* infections varies widely, ranging from mild fluid and electrolyte disorders, transient and mild glomerulonephritis, to acute kidney injury (AKI).

Plasmodium malariae: quartan malarial nephropathy

Introduction and epidemiology

Although the association between malaria and nephropathy was suggested two centuries ago, the first definite causal relationship between *P. malariae* and nephrotic syndrome was reported by Giglioli (1930). Nephropathy has been reported from British Guyana, Uganda, Nigeria, Kenya, Ivory Coast, Sumatra, New Guinea, and Yemen. The precise incidence of glomerular disease associated with *P. malariae* is not known. However, areas of the world with a high incidence of nephrotic syndrome overlap with those where *P. malariae* exists. A significant relationship between malaria infection and the nephrotic syndrome was shown by Gilles and Hendrickse (1963) in nephrotic children: 88% of the nephrotics tested positive for malaria compared to 24% of non-nephrotic children. *P. malariae*-induced nephropathy was observed in 25–33% of children with nephrotic syndrome (Abdurrahman et al., 1990). Furthermore, the admission rate for nephrotic syndrome significantly decreased in Guyana after the extermination of endemic *P. malariae* infection (Giglioli, 1972). These observations suggest the relationship of nephropathy with *P. malariae* infection but a cause and effect relationship has not been proven. Doe et al. (2006) reported a scarcity of data on quartan malaria nephrotic syndrome in recent literature. Additionally, in the absence of any unique pattern of nephrotic syndrome in African children, this paradigm of nephrotic syndrome induced by quartan malaria in the present era has been questioned (Ehrich and Eke, 2007). However, it cannot be ruled out that improved nutritional status and a better supply of antimalarials may have reduced the number of cases of quartan malaria nephrotic syndrome.

Clinical features

Renal involvement is indicated by the appearance of proteinuria, which typically develops several weeks after onset of quartan fever. Quartan malarial nephropathy occurs predominantly in children and young adults with a peak incidence at 5–8 years of age (Barsoum, 2000). Oedema and ascites are prominent features and are accentuated by concomitant protein–energy malnutrition. Hypoalbuminaemia is usually profound. The blood pressure is normal at onset of disease, but increases once renal failure sets in. Proteinuria is non-selective in 80% of patients (Hendrickse et al., 1972). A full-blown nephrotic syndrome is seen in about half of the cases. Microscopic haematuria is noted occasionally. In contrast to other causes of nephrotic syndrome, serum cholesterol tends to be normal or low, reflecting concomitant malnutrition. Serum complement (C3) is within normal range. *P. malariae* parasitaemia is detected in early stages in about 75% of cases (Chugh and Sakhuja, 1986). Spontaneous remission of established nephropathy is rare, and most patients progress to end-stage renal failure over 3–5 years even after successful eradication of the infection (Gilles and Hendrickse, 1963).

Pathogenesis

The role of *P. malariae* in the aetiology of human glomerulonephritis is based on experimental work suggesting that parasitic antigens and host antibodies are the culprits in glomerular damage. Demonstration of malarial antigen in the deposits and the bindings of specific antibody to circulating malarial antigens suggest an immunological basis. Since *P. malariae* can persist for long periods in the liver, continuous supply of antigen from the liver may contribute to perpetuation of renal lesions (Ehrich and Eke, 2007).

Subendothelial immune complex deposition in Rhesus monkeys (*Macaca mulatta*) infected with *P. inui* indicates that circulating immune complexes cause glomerulonephritis. In mice infected with *P. berghei*, malarial antigen first appears in circulation 3 days after infection. The antigen along with immunoglobulins and complement can be detected along the glomerular capillary walls and in mesangium from the seventh day (Boonpucknavig et al., 1973). These findings indicate the need for antigen processing after release from the erythrocytes prior to the formation of immune complexes

and deposition in the glomeruli. In the 1970s, development of immune complex glomerulonephritis with a nephrotic syndrome in *Aotus* monkeys infected with *P. brasilianum* was regarded as the classical animal model for human quartan malaria nephrotic syndrome (Voller et al., 1973).

The circulating immune complexes can be of parasite origin or those released by malaria-induced cellular injury. Molecular mimicry has also been suspected (Elsheikha and Sheashaa, 2007). There is an increased prevalence of antinuclear antibody positivity among people living in endemic areas. Deposition of immune complexes results in complement activation and inflammatory response. The reason why only a small proportion of patients with *P. malariae* infection develop renal lesions and the factors that determine its progressive nature are not well understood, but a permissive role of environmental factors such as malnutrition and co-infection with Epstein–Barr virus have been suggested (Wedderburn et al., 1988).

Pathology

Light microscopy shows chronic progressive membranoproliferative glomerulonephritis, with segmental thickening of glomerular capillary walls caused by subendothelial deposition of periodic acid–Schiff and silver stain-positive fibrils arranged in a plexiform manner (Hendrickse et al., 1972; White, 1973). As the disease progresses, more capillaries become affected and the lesions extend to cause progressive narrowing and eventually obliteration of the lumina. Proliferative lesions such as mesangial hypercellularity and occasional crescents may be seen in adults. The tubulointerstitial changes include tubular atrophy and infiltration with lymphomononuclear cells.

Hendrickse et al. (1972) divided the histological lesions into three grades of increasing severity. In grade I, less than one-third of glomeruli show localized capillary-wall thickening and segmental sclerosis; in grade II, 30–75% of glomeruli are affected, often with diffuse thickening of capillary walls and sclerosis producing a 'honeycomb' appearance; and in grade III > 75% of glomeruli are involved with prominent tubular atrophy and interstitial inflammation.

Immunofluorescence shows deposits containing immunoglobulin (Ig)-M, IgG, C3, rarely IgA, and malarial antigens in mesangial and subendothelial areas. *P. malariae* antigen is detected in about 25% of cases (Ward and Kibukamusoke, 1969; Houba, 1979). Three patterns of immune deposit can be encountered. The most common is a coarse, granular deposition of IgG3 along the capillary walls. A smaller number show diffuse, fine, homogeneously distributed IgG2 deposits without complement, and a mixed pattern is observed in the remaining cases. Electron microscopy reveals subendothelial deposits of basement membrane-like material. Intramembranous deposits are noted occasionally. Hendrickse et al. (1972) described mesangial lacunae of electron-dense material with a density similar to the basement membrane.

Treatment and outcome

Treatment of quartan malarial nephropathy is highly unsatisfactory. In general, nephrotic syndrome does not respond to chloroquine and pyrimethamine (Gilles and Hendrickse, 1963; Trang et al., 1992). Remission of renal abnormalities occurs only in those patients with mild proliferative changes (Houba, 1979).

Corticosteroids are ineffective in inducing remissions and a good response indicates concomitant minimal change disease. Cyclophosphamide may induce remission in steroid-resistant patients with mild lesions, but there is no improvement in overall survival (Adeniyi et al., 1979). No difference in outcome has been observed between the three grades of injury (Hendrickse et al., 1972). Renal failure, infections, and malnutrition are the common causes of death.

Plasmodium falciparum: acute kidney injury

Introduction and epidemiology

The contribution of malaria to the overall hospital admissions for AKI varies from 2% to 39% in different geographic regions from where malaria is reported. This variation is dependent on the local rates of malarial transmission. AKI is seen predominantly in non-immune adults from areas of low intensity of transmission (Mishra and Das, 2008).

Only a few reports of malarial AKI are available from Africa, an endemic area with intense malaria transmission. Transmission intensity is not uniform throughout the continent, and a higher incidence of AKI is reported in semi-immune children. In a study from Addis Ababa, 21% of 136 consecutively treated adult AKI patients had falciparum malaria (Zewdu, 1994).

The proportion of AKI is several-fold higher when malaria develops in non-immune individuals. AKI occurs in 25–30% of Europeans with complicated falciparum malaria as compared to 1–4.8% of those living in endemic areas. AKI was a frequent accompaniment in patients with severe falciparum malaria reported from Austria and the Netherlands (Gerritsen et al., 1992: Losert et al., 2000). Almost all patients with fatal cases had AKI and reported a history of recent travel to malaria-endemic areas.

A large number of reports on malarial AKI are from South East Asia and the Indian subcontinent where malaria transmission generally is low. A significant increase in the incidence of AKI in falciparum malaria has been reported from all across India. AKI as a complication of falciparum malaria increased from 6% in 1982 to 35% in 2002 in a centre from eastern India (Panda et al. 2003). A high incidence of AKI also has been reported from Pakistan, Singapore, Malaysia, Thailand, and Vietnam (Mishra and Das, 2008).

Clinical features

Malarial AKI may present either as a component of multiorgan dysfunction or as AKI alone. When part of multiorgan failure, AKI is usually present at the time of presentation and carries a poor prognosis. In the other subset, it occurs after other complications have subsided and has a better outcome. At this stage, the parasites are no longer present in the peripheral blood, making it difficult to establish the diagnosis of malaria. A high index of suspicion and the use of alternative diagnostic tools, such as antibody-based card tests that detect *P. falciparum*-specific histidine-rich protein 2 or lactate dehydrogenase antigens and immunochromatographic tests are of paramount importance. Oliguria may be seen in up to 75% of patients and may persist for 3–10 days (Mishra and Das, 2008).

About half the patients with renal failure develop jaundice (Wilairatana et al., 1994). In contrast, renal impairment is observed

in 10% of patients with hyperbilirubinaemia. The hyperbilirubinaemia is predominantly unconjugated owing to haemolysis. Anaemia and thrombocytopenia may be seen as a result of disseminated intravascular coagulation initiated by the rheological abnormality in severe malaria (Mishra and Das, 2008). Cerebral malaria is often associated with AKI, and is an important predictor of mortality (Mishra et al., 2007).

Pathogenesis

The precise mechanism responsible for AKI in falciparum malaria is not clearly known. Complications are caused by the interaction of the parasite with the host causing mechanical, immunological, and humoral responses. Hypotheses include mechanical obstruction of the renal microcirculation by parasitized red blood cells (RBCs), exaggerated host immune response mediated through cytokines and reactive oxygen intermediates (ROIs), nitric oxide (NO), and hypovolaemia (Fig. 183.1).

Mechanical obstruction by parasitized RBCs

Cytoadherence of parasitized RBCs to the endothelial cells of host organs along with rosette formation is an important consequence of severe malaria. Parasitized RBCs get sequestered in deep vascular beds of vital organs including kidneys (Kyes et al., 2001; Pongponratan et al., 1991). Parasite proteins called 'variant surface antigens' expressed on the surface of parasitized RBCs mediate adhesion to the endothelial cell surface receptors (Magowan et al., 1988). Autopsy studies showed that the frequency of parasitized RBC sequestration in renal vessels of patients dying from AKI were significantly higher than those without AKI (MacPherson et al., 1985).

Exaggerated host immune response

The host–parasite interaction results in immunologic and humoral responses. Primarily designed to eliminating the parasite, the response also injures host tissues. Excessive release of cytokines, ROIs, and NO may be responsible for manifestations of severe malaria (Greve et al., 1999; Griffiths et al., 2001). High concentrations of ROI and a depleted antioxidant defence system have been observed in patients with malaria (Nanda and Das, 2000). The effect of NO depends on its time of release and the type of isoform released. While early increase of NO helps the T helper (Th)-1 response to control parasitaemia (Nahrevanian and Dascombe, 2001), late increase of NO production in the liver and spleen appear to have pathological consequences (Nahrevanian and Dascombe, 2002).

Hypovolaemia and disturbed renal microcirculation

Low intake of fluids, loss of fluids because of vomiting, and pyrexial sweating causes dehydration and renal ischaemia. Inflammatory activation leads to generalized vasodilatation and decreased peripheral resistance, a situation akin to septicaemia. Vasodilatation leads to activation of sympathetic nervous system, renin–angiotensin–aldosterone axis activation, and release of vasopressin. These compensatory mechanisms may worsen the renal perfusion leading to overt kidney failure (Cumming et al., 1988; Benedict and Rose, 1992).

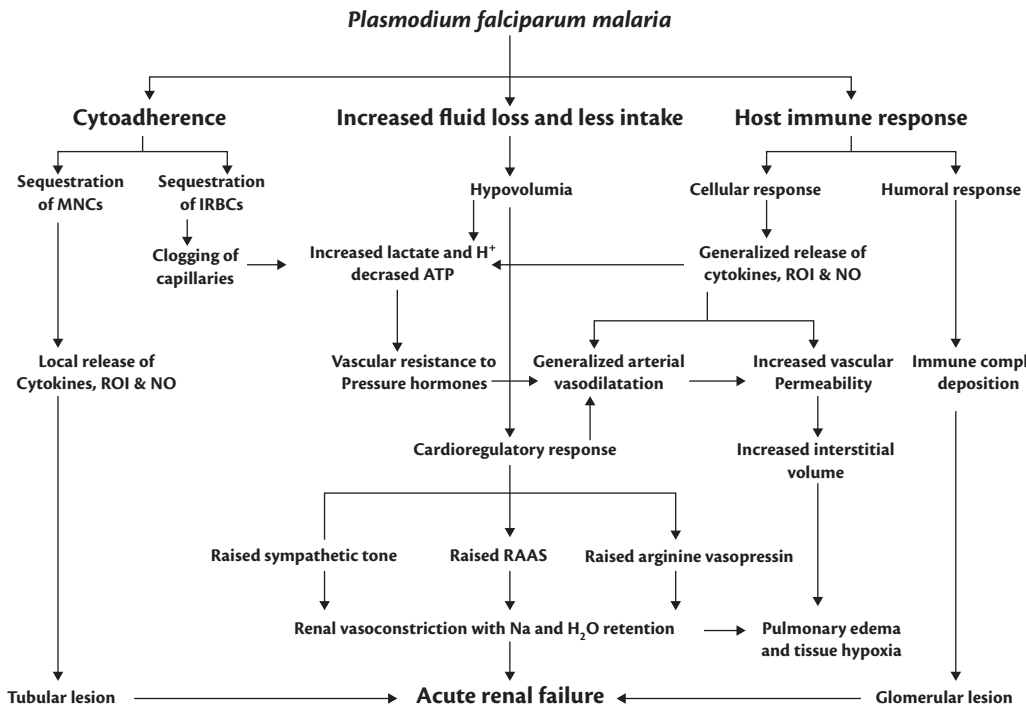

Fig. 183.1 Mechanism of acute kidney injury. H^+ = hydrogen ion; IRBCs = infected (parasitized) red blood cells; MNCs = mononuclear cells; NO = nitric oxide; RAAS = renin–angiotensin–aldosterone system; ROI = reactive oxygen intermediates.
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Pathology

Acute tubular necrosis (ATN) is the commonest histological finding. Tubular cells show a variety of changes ranging from cloudy swelling to cellular necrosis. Other changes include deposits of haemosiderin, haemoglobin casts in the tubular lumen, and interstitial oedema with mononuclear cellular infiltration. The venules may contain parasitized RBCs and rosettes. Mononuclear cells in glomerular and peritubular capillaries with phagocytosed malarial pigment have been observed (Nguansangiam et al., 2007). Acute cortical necrosis may rarely occur (Baliga et al., 2008). Acute interstitial inflammation is a common histopathological association, but isolated interstitial nephritis is uncommon.

Treatment and outcome

Renal failure resolves over days to weeks. The overall mortality rate among those with renal failure ranges from 15% to 50% (Mishra and Das, 2008). Risk factors associated with mortality include late referral, short acute illness, high parasitaemia, oliguria, hypotension, severe anaemia, hepatitis, and acute respiratory distress.

Treatment includes institution of antimalarials, maintenance of fluid and electrolyte balance, renal replacement therapy as indicated, and treatment of associated complications. All patients with severe *P. falciparum* infection should be presumed to have chloroquine-resistant infection. Cinchona alkaloids (quinine or quinidine) or artesunate are the mainstay of treatment because of their activity against chloroquine-resistant strains. Quinine often causes hyperinsulinaemia and hypoglycaemia and many centres recommend administration of a continuous infusion of 5–10% dextrose to all patients. The dose is 10 mg/kg every 8 hours. The dose should not be modified in the initial 48 hours, even in the presence of AKI, but should be reduced to two-thirds after that time. Careful attention needs to be given to the rate of infusion, electrocardiographic monitoring, and prevention of fluid overload. Prolonged QT interval, atrial or ventricular ectopic beats, heart block, and hypotension should be looked for in patients treated with quinine. Oral therapy should be started as soon possible. The total duration of therapy is 7 days. The introduction of artemisinin derivatives has improved the survival rates of patients with severe malaria. These drugs clear parasitaemia rapidly and are practically devoid of side effects (Dondorp et al., 2005; Jones et al., 2007). Moreover, no dosage modification is needed in the presence of renal or hepatic dysfunction. Intravenous artesunate is given at a dose of 2 mg/kg/body weight at 0, 12, and 24 hours, and then once daily for a total of 7 days.

Plasmodium falciparum: glomerulonephritis

Glomerulonephritis associated with falciparum malaria is transient and mild, and resolves within 4–6 weeks of eradication of infection. Proteinuria, microhaematuria, and casts are noted in 20–50% of infected patients (Rabenantoandro et al., 1994). Full-blown nephrotic syndrome and acute nephritis are rarely seen. Hypocomplementaemia is common and circulating immune complexes along with *P. falciparum* antigen can be demonstrated during the acute phase (Barsoum, 1998).

Pathology

Glomerular lesions are detected in approximately one-fifth of autopsies on patients with falciparum malaria. Main findings are prominent mesangial proliferation, modest matrix expansion, and occasional basement membrane thickening. Immunofluorescence shows finely granular IgM and C3 deposits along the capillary walls and in the mesangium. Immune complexes containing *P. falciparum* antigen in the glomerular basement membrane and mesangium can be observed. Electron microscopy shows subendothelial and mesangial electron-dense deposits along with granular, fibrillar, and amorphous material (Barsoum, 2000).

Plasmodium vivax: acute kidney injury

AKI due to *P. vivax* alone or as a result of mixed infection due to vivax and falciparum has been reported mainly from the Indian subcontinent (Prakash et al., 2003). Renal ischaemia results in ATN. Rare manifestations include thrombocytopenia, encephalopathy, and disseminated intravascular coagulation (Kaur et al., 2007; Song et al., 2007). Generally the outcome is better than that of falciparum infection.

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CHAPTER 184

Leishmaniasis and trypanosomiasis

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Leishmaniasis

Introduction and epidemiology

Leishmaniasis, an infectious disease caused by obligate intramacrophage protozoa, is transmitted through the bite of infected female sandflies. More than 20 leishmanial species are responsible for four main clinical syndromes: cutaneous leishmaniasis, mucocutaneous leishmaniasis, visceral leishmaniasis (also known as kala-azar), and post-kala-azar dermal leishmaniasis (Chappuis et al., 2007).

These species are distributed in China, the Mediterranean basin, South America, Africa, the Middle East, and the Indian subcontinent. Cutaneous and mucocutaneous leishmaniasis are usually caused by *Leishmania tropica* and *L. brazilliensis* while visceral leishmaniasis is caused by the *Leishmania donovani* complex which includes three species viz. *donovani, infantum*, and *chagasi*; the latter two are considered identical (Chappuis et al., 2007). Until recently, the public health impact of leishmaniasis was grossly underestimated. As per the World Health Organization, in the past 10 years, the endemic regions have been spreading and there has been a sharp increase in the number of cases. About 2 million new cases occur annually, with about 12 million people currently infected. Around 90% of all visceral leishmaniasis cases occur in Bangladesh, Brazil, India, Nepal, and Sudan.

Clinical features

Renal involvement can be seen in visceral leishmaniasis. After an incubation period of between 2 and 6 months, the disease presents with malaise, fever, fatigue, and weight loss. The intense parasitism of the reticular endothelial system causes hepatosplenomegaly, anaemia, leucopenia, and thrombocytopaenia as well as hypergammaglobulinaemia. Kidney involvement manifests as proteinuria, haematuria, and leucocyturia. Acute nephritic syndrome and nephrotic syndrome have also been described. Kidney involvement is generally mild and reversible with the treatment of infection (Clementi et al., 2011). Abnormalities in glomerular filtration rate (GFR), urinary concentration, and acidification have been observed in patients with chronic visceral leishmaniasis (Lima et al., 2007). Impaired urinary concentration capacity was seen in 68% of patients, and incomplete and complete distal renal tubular acidosis was seen in 34% and 30% of patients, respectively. Proximal tubular dysfunction may also be seen (Agenor Araujo Lima Verde et al., 2009). Tubular dysfunction may result in hyponatraemia, hypokalaemia, hypocalcaemia, hypomagnesaemia, and hypouricaemia.

Decreased GFR could be due to fluid loss, hypotension, immune-mediated glomerular disease, or nephrotoxicity of agents used to treat leishmaniasis. Acute kidney injury (AKI) has been reported to be present in 34% of patients prior to initiating therapy (Daher et al., 2008; Oliveira et al., 2010). Mortality in visceral leishmaniasis with AKI was 10-fold higher than in those without AKI. Factors predisposing to AKI include male sex, advanced age, jaundice, and amphotericin B use (Oliveira et al., 2010).

Visceral leishmaniasis frequently affects immunocompromised individuals such as HIV-infected patients and organ transplant recipients (Antinori et al., 2008). Nephrotic syndrome with irreversible AKI has been reported in HIV-infected patients possibly related to glomerular AA amyloid deposits (Navarro et al., 2006). Tubulointerstitial nephritis resulting in AKI has also been described in a kidney transplant recipient (Dettwiler et al., 2010).

Pathogenesis and pathology

Immune complex deposition, T cells, and adhesion molecule activation have been shown to be important mediators of injury in the glomerulonephritis. Prianti et al. (2007) observed a mesangial proliferative pattern of glomerulonephritis in *Leishmania chagasi*-infected mice. The presence of immunoglobulin G deposits and the absence of C3b deposits in the glomeruli suggested that immunoglobulins may be involved in the pathogenesis of glomerular injury while complement did not seem to play an important role in the disease. Histology reveals diffuse proliferative or mesangioproliferative glomerulonephritis (Dutra et al., 1985). Segmental necrotizing glomerulonephritis with crescents, interstitial nephritis, and amyloidosis have also been reported (Chaigne et al., 2004; Navarro et al., 2006; Dettwikler et al., 2010).

Treatment

Amphotericin B has replaced pentavalent antimonial compounds (stibogluconate) due to increasing treatment failure rates, but amphotericin is nephrotoxic. Paromomycin is as effective as amphotericin with less nephrotoxicity but has more adverse effects.

Trypanosomiasis

Two forms of trypanosomiasis are known. The African form (also known as sleeping sickness), caused by *Trypanosoma brucei* is

transmitted to humans by tsetse fly (*Glossina* spp) bites. *T. brucei gambiense* causes a chronic illness which may present after months or years as progressive meningoencephalitic illness, and *T. brucei rhodesiense* causes an acute febrile illness with neurologic and cardiac manifestations, anaemia, and disseminated intravascular coagulation that often ends fatally within a few weeks. The disease is mainly seen in non-immune tourists upon their return after a visit to the endemic area (Migchelsen et al., 2011)

The American form (Chagas disease) is seen in South America. It is caused by *T. cruzei* and transmitted by the faeces of reduvid bugs. Cardiac involvement in acute phase is due to myocardial parasitaemia. In the chronic phase, cardiac dilatation and arrhythmias as well as gut dysmotility resulting in megaoesophagus and megacolon are the result of autoimmune phenomenon.

AKI may be encountered during the terminal phases as a component of multiorgan failure in African trypanosomiasis. There is however no direct association of either form of trypanosomiasis with nephropathy in humans.

Mice infected by *T. brucei* or *cruzei* develop proliferative glomerulonephritis or mesangiocapillary glomerulonephritis (van Velthuysen et al., 1992). Immunoglobulin and complement deposits are observed in mesangial, subendothelial, and subepithelial regions. Antitrypanosomal antibodies have been detected in glomerular eluates. Serologic studies in monkeys showed high levels of circulating immune complexes and a reduction of serum C3 levels with normal C4 levels, suggestive of direct alternative complement activation by the parasitic antigens. Similar observations were made in a murine model, in which electron-dense deposits were also found in the mesangium and subendothelial space (Nagle et al., 1974).

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CHAPTER 185

Hepatitis B

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Introduction

A variety of glomerulonephritis (GN) have been reported to be associated with hepatitis B virus (HBV) infection. The strongest and most frequent association, particularly in children, is with membranous nephropathy (MN). An association between HBV infection and MN was first described four decades ago with detection of hepatitis B surface antigen (HBsAg) by indirect immunofluorescence in the renal tissue of a patient with MN (Combes et al., 1971). Though many subsequent reports supported this finding with epidemiologic and therapeutic data, HBV antigen staining in renal tissue to confirm HBV-GN remained a challenge. In a landmark study, different HBV antigens (HBsAg, HBeAg or HBcAg) were found to be associated with different morphologies, with HBeAg more with subepithelial and HBsAg more with mesangial immune complexes (Lai et al., 1994). When the diagnosis of HBV-GN was based only on the presence of detectable glomerular antigens, three distinctive morphologies could be identified: MN, membranoproliferative glomerulonephritis (MPGN), and mesangial proliferative glomerulonephritis with or without immunoglobulin A (IgA) deposits.

MPGN (type I and III) is the second most common GN reported to be associated with HBV infection (Lee et al., 1988; Lai et al., 1996). However, reports of HBV-associated MPGN prior to the detection of the hepatitis C virus (HCV) in 1989 have to be interpreted with caution, as these cases may have been due to undetected co-infection with HCV, which is now a well-established cause of MPGN type I.

Though less common and sometimes considered controversial (Iida et al., 1990; Chung et al., 1997), mesangial proliferative glomerulonephritis (non-IgA or with predominant mesangial IgA deposits, i.e. IgA nephropathy) has also been associated with HBV infection. After initial case reports (Nagy et al., 1979), Lai et al. (1988) described a higher prevalence of HBsAg amongst 122 patients with IgA nephropathy compared to the prevalence of HBsAg carrier state in the general population (17.2% vs < 0.01%). Besides the immunohistochemical localization of HBsAg and HBcAg in mesangial cells (Lai et al., 1994), HBV DNA could be detected in tubular and glomerular cells in a high proportion of patients with IgA nephropathy (Wang et al., 2003, 2005). Cases of successful treatment of mesangial proliferative GN/IgA nephropathy with antiviral therapy for HBV have been reported (Dhiman et al., 1999; Ozdamar et al., 2003) as well as no effect of antiviral therapy on the outcome (Sun et al., 2013).

Recent reports suggest an association with focal and segmental glomerular sclerosis (FSGS), which has been shown to respond to antiviral therapy (Khaira et al., 2009). Case reports of other forms of glomerulopathies (like minimal change disease and crescentic GN) in chronic HBV infection are most likely coincidental findings.

The causal relationship of hepatitis B with polyarteritis nodosa (PAN) has been widely confirmed ever since its first description in 1970 (Gocke et al., 1970), and evidence for the presence of chronic HBV infection became one of the 10 diagnostic criteria in the American College of Rheumatology (ACR) 1990 criteria for the classification of PAN (Lightfoot et al., 1990).

Though mixed cryoglobulinaemia/cryoglobulinaemic vasculitis is strongly linked with HCV, association with HBV infection has also been described, with reports of remission following antiviral therapy for chronic hepatitis B (CHB) (Enomoto et al., 2008; Enriquez et al., 2010). The classic expression of cryoglobulinaemia-associated renal disease is MPGN.

A summary of HBV-associated renal diseases is provided in Table 185.1.

Hepatitis B infection

HBV is a hepatotropic DNA virus that infects only humans and some non-human primates. The virion is a spherical double-shelled particle with an outer lipoprotein envelope containing the hepatitis B surface antigen (HBsAg) and an inner nucleocapsid of core antigen (HBcAg) in which viral polymerase and the partially double-stranded HBV genome are enclosed. Hepatitis B core antigen (HBcAg) is present exclusively in nuclei of infected hepatocytes and only the corresponding antibody circulates in blood. Generally, anti-HBc persists for life, irrespective of whether the infection resolves or becomes chronic. HBeAg is produced during active viral replication. After entering the host cell, the viral genomic DNA is converted in the nucleus to covalently closed circular DNA (cccDNA), which serves as a template for transcription of viral mRNAs, which in turn are used for viral replication through reverse transcription and the production of viral DNA polymerase and other viral proteins. The cccDNA remains intrahepatic even after resolved infection (seroconversion to anti-HBs, which occurs either spontaneously or after successful treatment), thus leading to a persistence of the infection bearing the potential of a reactivation.

The average incubation period is 90 days (range 6 weeks to 6 months). HBV DNA may be detected 30–60 days after infection. The first serological marker is HBsAg, becoming detectable within 3 weeks after the appearance of HBV DNA, with anti-HBc and then HBeAg appearing shortly afterwards. The risk of developing chronic infection, defined as the persistence of HBsAg in the blood for > 6 months, is dependent on the age and immune function of

Table 185.1 Renal disease associated with HBV infection

Renal disease	Histopathological findings	Clinical presentation	Treatment
HBV-GN			*For all HBV-GN* *Antiviral therapy* for HBV *Supportive therapy* as with other idiopathic nephrotic or nephritic syndromes, e.g. ◆ control of proteinuria with angiotensin converting-enzyme inhibitors or angiotensin receptor blockers ◆ control of hypertension with further agents if not controlled with above ◆ lipid-lowering therapy in case of hyperlipidaemia ◆ diuretics for volume overload *Immunosuppressive therapy* (low-dose corticosteroids) if antiviral therapy alone not sufficient
Membranous nephropathy (MN)	Similar to primary MN with subepithelial immune complexes, mesangial abnormalities are more common in secondary MN Principal antigens detected on immunhistochemical (IHC) testing—HBeAg in the subepithelial deposits	*Children:* More benign course, progression to renal failure and ESRD uncommon (< 5%), nephrotic syndrome or asymptomatic proteinuria, microhaematuria, normal transaminases *Adults:* Renal dysfunction, hypertension, and elevated transaminases seen more frequently, progression to renal failure in 25–30% and to ESRD in up to 10% or higher	
Membranoproliferative GN (MPGN) (types I and III)	Similar to idiopathic MPGN, immune deposits in both the mesangium and subendothelial space with mesangial proliferation and extension into the subendothelial zone, with both abnormal and normal segments of the glomerulus which is typical of secondary forms of MPGN Principal antigens detected on IHC—HBeAg along the capillary basement membrane and HBsAg in the mesangial deposits	Nephritic syndrome	
Mesangial proliferative GN with or without IgA deposition	Similar to idiopathic mesangioproliferative GN with immune complexes in mesangium (IgA deposits in IgA nephropathy) Principal antigen detected on IHC—HBsAg in the mesangial deposits	Nephritic syndrome	
HBV-associated vasculitis			
Polyarteritis nodosa (PAN)	Diagnostic renal biopsy not usually performed. Lesions of renal ischaemia or infarction, or fibrinoid necrosis of medium sized arteries may be present	Mainly in young patients < 40 years old, manifests in < 12 months after onset of HBV infection, features of systemic vasculitis similar to those in non-HBV classical PAN Renal: loin pain, gross or microscopic haematuria, moderate proteinuria, slowly progressive renal insufficiency, hypertension, acute kidney injury uncommon	Antiviral therapy for HBV, corticosteroids and/or plasma exchange for severe disease
Mixed cryoglobulinaemia	Histological picture of MPGN with some intracapillary thrombi containing cryoglobulin precipitates	Renal: isolated proteinuria and haematuria are more common than nephrotic syndrome, nephritic syndrome or acute kidney injury. Other: Meltzer triad, i.e. purpura, arthralgia, and weakness, myalgia, peripheral neuropathy, cutaneous vasculitis (erythematous macules or papules, ulcers particularly in lower extremities)	Antiviral therapy for HBV, immunosuppressive therapy

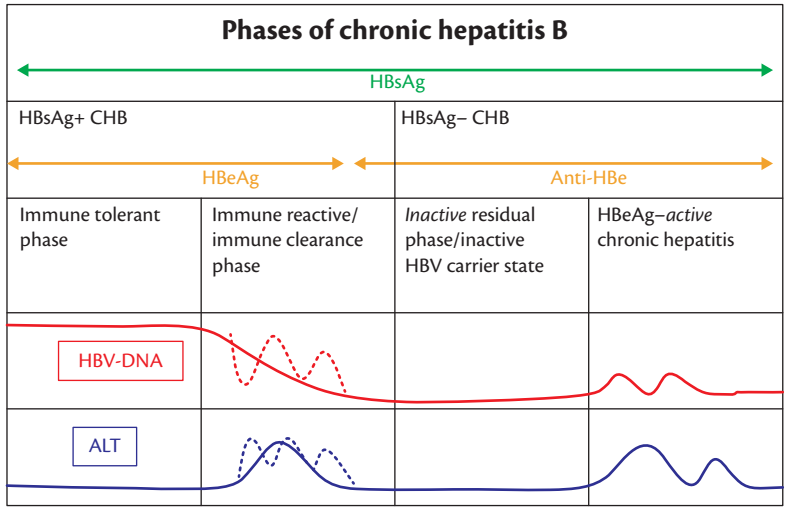

Fig. 185.1 The natural history of chronic hepatitis B infection.

the patient. The likelihood of an HBV infection becoming chronic decreases with the age at which a person became infected. About 90% of infants infected during the first year of life, 30–50% of children infected between 1 to 4 years of age, and 10% of adults progress to chronic infection.

The natural history of CHB infection (defined as persistence of HBsAg for > 6 months) is classified into several phases (European Association for the Study of the Liver (EASL), 2012) (Fig. 185.1). An 'immune-tolerant phase' is typically seen in those infected as infants or children. HBsAg and HBeAg are detectable together with a high viral load of HBV DNA. The patients are asymptomatic, with normal transaminases and minimal histological changes. The transition to an 'immune-reactive/immune-clearance phase' can occur in young adulthood (15–35 years) or immediately in adult infection. Transaminases rise and histological activity increases, while HBV DNA levels fall. This may be accompanied by hepatic decompensation, culminating in the clearance of HBeAg and seroconversion to anti-HBe, with HBV DNA falling to low levels or disappearing.

Among HBeAg carriers with elevated alanine aminotransferase (ALT) levels, the rate of spontaneous HBeAg clearance averages 8–12% per year but is much lower in HBeAg carriers who are in the immune tolerant phase and in immunocompromised subjects. This is followed by the 'inactive residual phase/inactive HBV carrier state', with low HBV DNA levels, normal transaminases, and a low rate of HBsAg seroclearance. Patients with infection by HBV variants with nucleotide substitutions in the pre-core and/or basal promoter region remain HBeAg negative. These patients show signs of active hepatitis with fluctuating elevated transaminases and/or HBV DNA ('HBeAg-negative CHB') and are at a high risk of progression and developing complications of CHB.

Epidemiology

It is estimated that over one-third of the world's population has been exposed to the HBV, showing positive antibodies for HBcAg, and that > 350 million people worldwide have CHB (World Health Organization, 2008). HBV prevalence varies greatly in different parts of the world, being highly endemic (10–20% HBsAg positive with up to 90–95% anti-HBc positive) in parts of Asia, Africa, South America, and the Arctic (World Health Organization, 2008). In countries with a high prevalence, most infections occur during childhood via vertical and horizontal transmission, while in countries with a low prevalence (e.g. Europe, United States, and Australia) infection usually occurs during adolescence or adulthood (either parenterally or via sexual contact).

Extrahepatic manifestations are seen in about 10% of CHB patients (Han, 2004). The reported prevalence of HBV infection in patients with GN ranges between 0.1% and 25% (Amarapurkar and Amarapurkar, 2002). HBV-MN is more common among children (with a strong male predominance) and represents the most common cause of nephrotic syndrome in children in endemic countries (Han, 2004). In low prevalence countries, HBV-associated MN is rare at all ages, and the male predominance is less pronounced (Bhimma and Coovadia, 2004). The decreasing incidence of HBV infection after the implementation of vaccination programmes correlates with dropping incidence rates of HBV-associated MN (Xu et al., 2003; Liao et al., 2011).

In contrast to MN, HBV-PAN is relatively more frequent in patients from low-endemic regions like Europe and North America (Chan and Kowdley, 1995). PAN is a rare disease with prevalence rates up to 3 cases per 100,000 and can be as high as 7.7 cases per 100,000 in populations where HBV is endemic (McMahon et al., 1989). Before the implementation of mandatory screening of blood donors and vaccination programmes, 30–50% of all PAN patients had an active HBV replication. Current HBV prevalence rates in PAN patients are reported at 5% which is still higher than the background prevalence in the general population (Marcellin et al., 1991).

Clinical features

The clinical course and prognosis of HBV-MN differs between children and adults. Children typically are in the immune-tolerant phase of CHB infection. Clinically, they present with nephrotic syndrome, although asymptomatic cases detected on routine urine screening can also be seen. The glomerular filtration rate (GFR) is usually normal or mildly reduced. Microhaematuria is seen more frequently in children than in adults (Lai and Lai, 2006). In adults,

HBV-MN manifests with proteinuria. Associated renal dysfunction, hypertension, and elevated transaminases are seen more frequently whereas haematuria is less frequent compared to children (Bhimma and Coovadia, 2004; Han, 2004). Spontaneous remission, associated with appearance of anti-HBe, is seen in 95% of in paediatric patients and 30–60% adults (Bhimma and Coovadia, 2004). A series in Hong Kong reported renal failure in approximately 30% and progression to end-stage renal disease (ESRD) in 10% of the patients in 5 years (Lai et al., 1991). A comparison of 119 HBV-MN patients with 143 patients with idiopathic MN showed a higher percentage of renal insufficiency (74% vs 36%) in patients with HBV-MN (possibly related to the higher presentation of histologically atypical MN including mesangial proliferation), though the renal survival rates did not differ between the two groups (Li et al., 2012).

The manifestations of HBV-associated MPGN are similar to those of idiopathic MPGN. Patients typically present with nephritic syndrome, hypertension, and reduced GFR. Some patients may have associated mixed cryoglobulinaemia, with systemic symptoms of cryoglobulinaemic vasculitis.

HBV-PAN typically affects patients under the age of 40. It usually becomes manifest within 12 months of the HBV infection, with a mean of 4 months (Trepo and Guillevin, 2001; Pagnoux et al., 2006). Compared to patients with non-HBV-associated PAN, HBV-PAN patients tend to have more severe disease (Pagnoux et al., 2010). Peripheral nerve involvement, orchitis, gastrointestinal manifestations (especially those requiring surgery), cardiomyopathy, and renal arteritis resulting in hypertension are more frequent in HBV-PAN (Trepo and Guillevin, 2001; Pagnoux et al., 2006, 2010).

Prognosis can be evaluated by using the French Five Factor Score (FFS) (Guillevin et al., 2011), which in its 2009 version includes factors like age, renal insufficiency, cardiac insufficiency, and/or gastrointestinal involvement for evaluation of PAN. Once remission has been obtained, patients with HBV-PAN have much lower relapse rates (6%) than non-HBV-PAN patients (Pagnoux et al., 2006, 2010). HBV-PAN does not recur after sustained seroconversion and suppressed viral replication.

Pathogenesis

Kidney disease is seen only in a subset of those with HBV infection, suggesting that host factors, such as immune system responses and genetic background and/or environmental factors determine the disease manifestation (Bhimma and Coovadia, 2004).

Since the initial descriptions, HBV-GN and PAN have been thought to be immune-complex mediated. Trapping of circulating immune complexes, composed of viral antibodies and antigens, in the glomeruli (HBV-GN) or medium-sized vessels (HBV-PAN) was considered to be the main pathogenic mechanism (Oldstone and Dixon, 1971; Kohler et al., 1974). This paradigm was challenged by observations that circulating immune complexes are also seen physiologically and occur more often than the extrahepatic disease, and that extrahepatic syndromes can occur even in the absence of immune complexes (Dienstag, 1981). Additionally, HBV components like the HBsAg are too large to pass through the glomerular basement membrane. Therefore, as an alternative explanation, the generation of *in situ* immune complexes (formed by antigens deposited in the renal tissue combining with antibodies that also enter the glomerulus) was proposed (Couser and Salant, 1980). However, in the last decade, HBV DNA, RNA, cccDNA and even complete viral particles have been identified in renal tubular cells suggesting that HBV-associated renal tissue injury is not only immune-complex mediated but rather due to cytopathic effects of the virus, which could result from either (a) direct renal cell toxicity of the virus or (b) indirect effects of virus-induced mediators, cytokines, or immunological effector mechanisms (Bhimma and Coovadia, 2004; Ren et al., 2006). Recent experimental studies have suggested a possible role of innate immunity and signalling pathways in immune inflammatory response and renal cell toxicity associated with HBV-GN (He et al., 2013; Zhou et al., 2013).

Diagnosis

While the diagnostic criteria for HBV-PAN were established by the ACR in 1990 (Lightfoot et al., 1990), no international diagnostic criteria have yet been established to confirm the aetiologic role of HBV in GN. The diagnostic standards for HBV-MN developed by the Chinese Medical Association (Chinese Medical Association, 1990) are as follows:

1. Typical histological picture with immunohistochemical detection of HBV antigens or HBV-DNA measured by PCR in the renal tissue (Fig. 185.2)

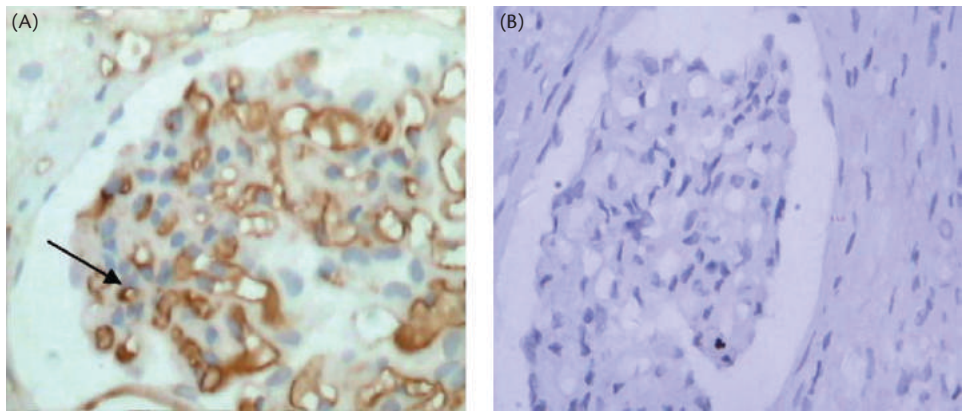

Fig. 185.2 HBsAg as detected in renal tissue by immunocytochemistry in HBV-associated glomerular disease: (A) HBsAg positive and (B) HBsAg negative.
Adapted from Chen et al., *Clinical Infectious Diseases*, 2012, 55/9, by permission of Oxford University Press.

2. HBsAg-positive serum/presence of active viral replication
3. Exclusion of other secondary glomerular diseases and lupus nephritis.

Testing for hepatitis C, hepatitis D, and HIV should be undertaken to rule out co-infections with these viruses.

However, since the techniques to detect the deposition of viral antigens in the kidney may not be routinely available, the diagnosis may be presumptively established based on assessment of viral replication, a typical histological pattern, and compatible clinical picture.

Treatment

General treatment of HBV infection

CHB infection can be treated either with subcutaneously administered (pegylated) interferon alpha (IFN-α) or with orally available nucleoside/nucleotide analogues (NUCs). Goal of treatment is the complete suppression of HBV-DNA (virological response), with durable HBeAg seroconversion to anti-HBe in HBeAg-positive patients (serological response) as a desirable endpoint and durable HBsAg seroconversion to anti-HBs as an ideal endpoint. However, this ideal endpoint is rarely achieved (Lok and McMahon, 2009; EASL, 2012). The first drug to be approved for CHB therapy was IFN-α in 1991. Since then, five oral NUCs have become available: lamivudine (LAM) in 1998, adefovir (ADV) in 2002, entecavir (ETV) in 2005, telbivudine (LdT) in 2006, and tenofovir (TDF) in 2008. The pegylated IFN-derivate PEG-IFN was approved in 2005. Advantages of IFN-α therapy include a finite duration of treatment with possible sustained response off-therapy and absence of any drug resistance. Disadvantages include adverse effects (e.g. depression, flu-like symptoms, neutropenia, and thrombocytopenia) and contraindications to treatment, such as decompensated liver cirrhosis or kidney transplantation. Guidelines on general CHB treatment recommend patients to be first evaluated for the possibility of IFN-α treatment. High baseline transaminases combined with low HBV-DNA levels, a histological high-grade inflammatory activity, and virus genotype A suggest the likelihood of good response.

In comparison to IFN, NUCs, which suppress HBV replication through inhibition of viral DNA polymerase, are efficient, well tolerated, easily administered, and have fewer contraindications, but often require long-term treatment and can result in the selection of drug-resistant HBV strains. LAM was the first approved NUC, and is now available in generic form. Its major disadvantage is very high resistance rates (70% after 5 years of therapy), with the attendant risk of hepatic decompensation following the breakthrough. ETV and TDF are third-generation NUCs with a high genetic barrier to resistance. No resistance with virological breakthrough has yet been described for TDF ever since its introduction, the cumulative resistance rate for ETV has been reported to be 1.2% after 6 years. Current guidelines recommend either ETV or TDF as first-line therapy (Lok and McMahon, 2009; EASL, 2012). LAM is still used as first-line therapy in some countries for cost reasons. LAM as presumptive therapy before immunosuppression is recommended only for patients with a low risk of hepatic decompensation, that is, with a low viral load (HBV-DNA < 2000 IE/mL; 1 IE/mL = 5.6 copies/mL) and no signs for an advanced fibrosis/cirrhosis. Second-generation NUCs ADV and LdT are no longer recommended for first-line monotherapy (Lok and McMahon, 2009; EASL, 2012).

As NUCs are excreted by the kidney, dose adjustment for renal impairment is necessary (Table 185.2). A minimal decline in the

Table 185.2 Dose adjustment for NUCs in renal impairment[a]

Substance	Standard dose	Creatinine clearance mL/min				Available form and strength
Lamivudine (LAM)		30–50	15–30	5–15	< 5	Solution (5 mg/mL) or Tablet 100 mg
HBV-monoinfection	100 mg	50 mg (first dose 100 mg)	25 mg (first dose 100 mg)	15 mg (first dose 35 mg)	10 mg (first dose 35 mg)	
HIV-coinfection	300 mg	150 mg	100 mg (first dose 150 mg)	50 mg (first dose 150 mg)	25 mg (first dose 50 mg)	
Adefovir (ADV)		20–49	10–19	Dialysis		Tablet 10 mg
	10 mg	10 mg every 48 hours	10 mg every 72 hours	No dosing recommended		
Entecavir (ETV)		30–49	10–29	< 10		Solution (0.05 mg/mL) or tablet 0.5 mg
Treatment-naive patients	0.5 mg	0.25 mg 0.5 mg every 48 hours	0.15 mg 0.5 mg every 72 hours	0.05 mg once daily or 0.5 mg every 7 days after dialysis.		
Patients in LAM-refractory patients	1.0 mg	0.5 mg	0.3 mg	0.1 mg once daily or 1 mg every 7 days after dialysis		
Telbivudine (LdT)		30–49	<30	Dialysis		Solution (100 mg/5 mL) or tablet 600 mg
	600 mg	600 mg every 48 hours	600 mg every 72 hours	600 mg every 96 hours after dialysis		
Tenofovir (TDF)		30–49	10–29	Dialysis		Tablet 300 mg
	300 mg	300 mg every 48 hours	300 mg every 72–96 hours	300 mg every 7 days after dialysis		

[a] The recommendations are only for adult patients.

GFR has been reported with all NUCs over long-term treatment except with LdT, which showed even an increase in the GFR from the baseline in a few studies (Chan et al., 2012; Gane et al., 2012; Wang et al., 2013). Nephrotoxicity seems to be more common with nucleotide analogues like ADV. The rate of renal tubular dysfunctions in HBV-infected patients treated with nucleotide analogues has been reported to be as high as 15% depending on the length of treatment and dose (Gara et al., 2012). TDF has been shown to cause proximal renal tubular dysfunction, a decline in the GFR, and very rarely acute kidney injury in HIV-infected patients (James et al., 2004). For HBV-monoinfected patients with no risk factors for renal disease, the decline in the GFR in ETV (Gish et al., 2012) treated patients smaller compared to untreated HBV patients (Mauss et al., 2011).

HBV-GN

Antiviral therapy

The severity of symptoms in HBV-GN is correlated with viral load (Wei et al., 2010) and reduction of viral load is correlated with remission of symptoms (Zhang et al., 2010). Most data on antiviral treatment exists for patients with HBV-MN (Conjeevaram et al., 1995; Lin, 1995; Tang et al., 2005). There are only anecdotal case reports or case series about antiviral treatment for HBV-associated MPGN, IgA nephropathy, or FSGS (Conjeevaram et al., 1995; Chung et al., 1997; Panomsak et al., 2006; Khaira et al., 2009; Sun et al., 2013). Moreover, data on antiviral drugs are mostly limited to first-generation HBV treatments like non-pegylated IFN-α and LAM.

Several meta-analyses (Fabrizi et al., 2006; Zhang et al., 2010; Yi et al., 2011; Zheng et al., 2012) of the controlled trials on the efficacy of antiviral treatment with IFN-α and/or LAM in children and adults with HBV-GN concluded that therapy improves HBeAg clearance, induces remission of proteinuria, and retards renal progression. However, besides the general possibility of publication bias in meta-analysis, and the small sample sizes, the recommendations are confounded by lack of adequately powered randomized controlled trials as well as the variations in treatment protocols in terms of dosage and duration.

Immunosuppressive therapy

Immunosuppressive therapy for HBV-GN without presumptive antiviral treatment should be avoided as it increases the risk of exacerbation and reactivation of HBV infection (Lai et al., 1990; Sayarlioglu et al., 2005). Furthermore, a meta-analysis of a few small, non-randomized studies showed no benefit of steroid use in HBV-associated nephropathies compared to controls (Zhang et al., 2010) in children and adults. However, a combination therapy with low-dose steroids and antiviral therapy could be beneficial for adult patients as shown in a recent meta-analysis (Zheng et al., 2012). In general, all HBsAg+ patients should receive pre-emptive antiviral therapy before (2 weeks before and no later as on the same day), during, and after (12 months) immunosuppressive therapy (EASL, 2012).

HBV-PAN

As in HBV-GN, antiviral agents improve outcome in HBV-PAN (Guillevin et al., 2005). However, while antiviral therapy alone is often sufficient in patients without life-threatening disease (Simsek and Telatar, 1995; Avsar et al., 1998) an additional immunosuppressive therapy is required in those with more severe disease manifestations (Guillevin et al., 2005). A short course of corticosteroids is recommended in the first few weeks (Guillevin et al., 2004; Guillevin and Pagnoux, 2007). A suggested regimen is as follows: methylprednisolone, 15 mg/kg/day intravenously for 1–3 days, followed by prednisone, 1 mg/kg/day orally for 7 days, tapered over the following 7 days (Guillevin et al., 2004). Antiviral therapy should be initiated simultaneously because of the potential for reactivation (Guillevin and Pagnoux, 2007). For patients with severe systemic manifestations, plasma exchange has been shown to be beneficial (Guillevin and Pagnoux, 2003), probably by removing circulating immune complexes. The European League Against Rheumatism (EULAR) guidelines suggest using a combination of antiviral therapy, plasma exchange, and glucocorticoids for hepatitis B-associated PAN (evidence level III) (Mukhtyar et al., 2009).

There are a few case reports and case series describing the treatment of HBV-PAN with first-generation antiviral substances (LAM and IFN-α). A retrospective study of 80 patients with HBV-PAN treated with a 2-week course of steroids + plasma-exchange + antivirals like IFN-α, LAM, and vidarabine (no longer available) showed a higher rate of remission (81%), associated with a higher rate of HBeAg seroconversion (> 60%) compared to historic controls treated with steroids +/− cyclophosphamide +/+ plasma-exchange and no antiviral therapy (Guillevin et al., 2005).

Recommendations and guidelines for antiviral treatment

The decisions on when and how to treat require a multidisciplinary approach between the nephrologist and the hepatologist. According to the KDIGO glomerulonephritis guideline (KDIGO, 2012), antiviral treatment is indicated for HBV-GN and should be conducted according to standard clinical practice guidelines for HBV-infection (evidence level 1c).

When to treat

Antiviral treatment is indicated in all cases with HBV-PAN because of its potentially life-threatening nature and in all adults with HBV-GN, as progression to ESRD is common in them.

In children, antiviral therapy is usually not recommended unless there is the risk of hepatic decompensation (Liaw et al., 2008). Treatment should be started only if ALT levels greater than twice normal persist for > 6 months (Lok and McMahon, 2009). Moreover, spontaneous remission of proteinuria with or without seroconversion is seen in about 50% over 30 months (Connor et al., 2003). Finally, fewer drugs are currently approved for use in children. These include conventional IFN-α, LAM, ADV (for children > 12 years), and ETV (for children > 2 years). Therefore, treatment should be reserved for subgroups with a higher risk of progression such as age > 6 years and longer disease duration (> 12 months) (Hsu et al., 1989; Wong et al., 1992).

How to treat

Antiviral therapy with oral NUCs is recommended for treatment of HBV-PAN (Guillevin et al., 2004; EASL, 2012) and for extrahepatic manifestations of HBV in general (EASL, 2012). Compared to IFN-α, LAM is more effective in more rapidly decreasing viral load in HBV-PAN and is effective in IFN-α non-responsive disease (Deleaval et al., 2001). Moreover, IFN-α may worsen autoimmune disease due to its immunomodulatory properties (Manns et al., 2006; EASL, 2012) and is less effective in combination with

immunosuppressive treatment. However, young patients with HBV-GN might benefit from IFN therapy because of the finite duration of treatment. Therapy with NUCs carries the risk of relapse after discontinuation (Tang and Lai, 2006). Even if HBe seroconversion occurs, the durability of this might be variable (Reijnders et al., 2010). Finally, the long-term safety of this treatment that might be required for decades has not been established.

Though studies on HBV-PAN and HBV-GN usually employed the first available NUC LAM, with only single case reports existing on the use of a third-generation agent (ETV) (Ikee et al., 2010; Naniwa et al., 2010; Sun et al., 2012; Yang et al., 2012), it seems plausible to recommend the use of third-generation NUCs with a high genetic barrier to resistance, by extrapolating data from the general HBV treatment.

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CHAPTER 186

Hepatitis C

Fabrizio Fabrizi

Introduction

Chronic hepatitis C virus (HCV) infection leads to hepatic fibrosis and eventually cirrhosis in 10–20% of patients. The latter subgroup is also at higher risk of hepatocellular carcinoma. In addition to these complications, HCV infection has been associated with extrahepatic disorders involving renal, dermatologic, haematologic, and rheumatologic systems. Renal manifestations were first reported by Johnson et al. (1993) who described eight patients with HCV infection and membranoproliferative glomerulonephritis (MPGN) and suggested that the glomerular disease resulted from HCV-containing immune complex deposition. Evidence has been subsequently accumulated showing that HCV is associated with immune complex glomerular diseases, including MPGN and membranous nephropathy (Fabrizi et al., 2002). In addition, HCV infection has been strongly linked with cryoglobulinaemia. Information on the exact prevalence of glomerular renal diseases in HCV infection remains unclear. A possible association between HCV and chronic kidney disease (CKD) would have global relevance because of the large burden of HCV. Worldwide, about 170 million individuals are chronically infected, and it is the commonest blood-borne infection and leading cause of liver transplantation in the developed world.

Hepatitis C virus and glomerular disease

There is increasing evidence for the association between HCV and glomerular disease in both native and transplanted kidneys (Cruzado et al., 2001; Ozdemir et al., 2006). These manifestations of HCV are uncommon and the available information on their frequency is mostly based on small observational studies. In a 5-year retrospective study on autopsies of patients (N = 114) infected with HCV, Gopalani and Ahuja (2001) reported 10 (8.7%) cases of glomerular diseases. In autopsies of patients with HCV-related liver disease, Arase et al. (1998) observed that the prevalence of MPGN was 11.2% (21/188). El-Serag et al. (2002) carried out a hospital-based case–control study among US male veterans hospitalized during 1992 to 1999 and identified 34,204 patients infected with HCV (cases) and 136,816 randomly selected patients without HCV (controls). Multivariate analysis showed that the HCV-infected patients had a significantly greater proportion of porphyria cutanea tarda (0.77% vs 0.06%; $P < 0.0001$), vitiligo (0.17% vs 0.10%; $P = 0.0002$), lichen planus (0.30 vs 0.13; $P < 0.0001$), and cryoglobulinaemia (0.57% vs 0.05%; $P < 0.0001$). There was a greater proportion of MPGN among patients with HCV (0.36% vs 0.05%; $P < 0.0001$), but not membranous glomerulopathy (0.33% vs 0.19%; $P = 0.86$). Based on this data, current Kidney Disease: Improving Global Outcome (KDIGO) (2008) guidelines recommend HCV screening for patients who have evidence of glomerulonephritis (GN).

The principal clinical manifestations of glomerular disease in HCV-infected patients are the proteinuria and microscopic haematuria with or without reduction in glomerular filtration rate (GFR). However, a large proportion of these patients remain asymptomatic. McGuire et al. (2006) performed renal biopsies at transplant surgery in a group of patients with HCV-associated cirrhosis and found that 25 of 30 had immune-complex GN, the most frequent being MPGN. The majority of these glomerular diseases were not clinically apparent. This study suggested a potentially large reservoir of kidney diseases in HCV-infected patients that could contribute to CKD in the general population. Screening for urinary abnormalities and alterations of kidney function in all HCV-positive patients is strongly recommended, particularly in those with cryoglobulinaemia. A kidney biopsy is necessary in those with urinary abnormalities to determine the histologic pattern of glomerular injury. Glomerular lesions have been described in the presence or absence of liver disease; however, all patients with HCV-associated GN have detectable HCV RNA in serum

Hepatitis C virus and renal insufficiency

Although transmission of HCV within dialysis units has been well described (Jadoul et al., 2004), the high prevalence of HCV in patients new to dialysis treatment is less appreciated. In a prospective observational study including 860 patients on regular haemodialysis, the prevalence of anti-HCV was 16.8% (Bergman et al., 2005). Patients new to dialysis had a prevalence of 14.4%. Age, gender, race, and drug abuse were independent predictors of anti-HCV positivity. The authors suggested that risk factors for HCV infection in patients receiving dialysis now may differ substantially from those identified 20 years ago. Nosocomial sources for anti-HCV are much less important because of the virtual elimination of HCV from the blood products, fewer transfusions due to erythropoietin use, and the practice of precautions against blood-borne pathogens. Rather, most patients on long-term dialysis may acquire anti-HCV before the initiation of dialysis.

Although the burden of illness related to HCV is higher among patients with end-stage renal disease, the impact of HCV infection on renal function in the general population is not clear. HCV is associated with cryoglobulinaemia and MPGN, and these, in turn, can lead to CKD. The available data on the association between HCV and kidney disease in the general population are conflicting but recent information supports an effect of HCV on kidney disease (Table 186.1). In a recent study based on the ERCHIVES

Table 186.1 Multivariate analysis for the association of hepatitis C to low eGFR: population-based surveys

Authors	Odds ratio (95% CI)	Country	Reference year
Tsui et al.	0.89 (0.49–1.62)	US	2006
Tsui et al.	2.80 (2.43–3.23)	US	2007
Dalrymple et al.	1.40 (1.11–1.76)	US	2007
Moe et al.	1.024 (0.90–1.15)	US	2008
Lee et al.	1.30 (1.20–1.42)	Taiwan	2010
Asrani et al.	0.92 (0.79–1.08)	US	2010
Butt et al.	1.30 (1.23–1.37)	US	2011

(Electronically Retrieved Cohort of HCV Infected Veterans) database, Butt et al. (2011) identified 18,002 US Veterans with HCV infection and 25,137 controls with estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m^2 at baseline between 2001 and 2006. HCV infection was associated with a higher risk of developing CKD stages 3–5 (hazard ratio (HR) 1.30; 95% confidence interval (CI) 1.23–1.37; P < 0.0001). Other risk factors for the development of uraemia included diabetes, hypertension, and dyslipidaemia. All these factors were less prevalent in HCV-infected patients compared with controls, emphasizing the importance of HCV on the occurrence of CKD. In another cross-sectional study of 54 966 subjects, prevalence of HCV and HBV infections was 9.4% and 9.9%, respectively and multivariate logistic regression showed HCV infection to be associated significantly with CKD (OR 1.26; 95% CI 1.17–1.38; P < 0.001) (Lee et al., 2010). HCV-positive serologic status also had a positive and significant association with proteinuria (odds ratio (OR) 1.14; 95% CI 1.003–1.300; P = 0.04). Two observational studies also demonstrated an independent relationship between HCV seropositive status and low eGFR (Dalrymple et al., 2007; Tsui et al., 2007). Finally, HCV infection has been shown to accelerate the progression of CKD in diabetics (Soma et al., 2000; Crook et al., 2005).

In contrast, at least three population-based surveys (Tsui et al., 2006; Moe et al., 2008; Asrani et al., 2010) found no association between HCV and CKD. In their multivariable model, Asrani et al. (2010) noted no link between HCV status and development of CKD (OR 0.92; 95% CI 0.79–1.08; P = 0.31). These results did not change when they used alternative definitions of renal disease progression. In a longitudinal analysis (Moe et al., 2008), the HR for development of CKD in HCV-infected subjects was 1.024 (95% CI 0.908–1.1.56, NS) after adjustment for age, baseline GFR, diabetes, hypertension, and HIV status.

It is difficult to explain these disparate data. Different populations were analysed, Moe et al. (2008) included patients seeking care in an urban inner city healthcare system whereas others (Dalrymple et al., 2007; Butt et al., 2011) enrolled patients followed up at the VA healthcare system, and Asrani et al. (2010) studied patients with private health insurance coverage from the United States. There was significant heterogeneity in the rate of HCV infection. Study designs were different: Tsui et al. (2007) and Asrani et al. (2010) performed longitudinal studies over 36 and 25 months, respectively, whereas other studies (Dalrymple et al., 2007; Lee et al., 2010) were cross-sectional. Additional inconsistency included the measures of renal function; Dalrymple et al. (2007) defined renal insufficiency as a serum creatinine level of ≥ 1.5 mg/dL (133 μmol/L), whereas others defined CKD as having an eGFR < 60 mL/min/1.72 m^2. Most studies performed serology for anti-HCV antibodies, but one study had HCV RNA (Butt et al., 2011). In addition, the results provided from these studies may not be generalizable to all races or geographical areas, as suggested from Table 186.1. There may have been other important confounders that were not adjusted for in the multivariate analyses. Finally, the possibility of missing data or insensitive codes for co-morbidity diagnoses in clinical databases cannot be ruled out.

Hepatitis C virus and proteinuria

The link between HCV infection and proteinuria is well established. At least four surveys (Liangpunsakul and Chalasani, 2005; Huang et al., 2006; Tsui et al., 2006; Lee et al., 2010) reported a significant and independent association between anti-HCV seropositive rate and proteinuria. The OR of anti-HCV seropositive status associated with proteinuria was 1.648 (95% CI 1.246–2.179; P = 0.003) in the report by Huang et al. (2006) who performed urine dipstick measurements in 9934 individuals in Taiwan, an endemic area for HCV (6.5%). Lee et al. (2010) found similar results in another endemic area (anti-HCV prevalence 9.4%; adjusted OR 1.14; 95% CI 1.003–1.300; P = 0.04) in 54,966 individuals in whom proteinuria was assessed twice.

In the Third US National Health and Nutrition Examination Survey (NHANES III) database, the anti-HCV antibody test was performed in 15,336 adults. HCV infection was independently associated with microalbuminuria in subjects without diabetes (OR 1.99; 95% CI 1.38–2.85; P = 0.008). This association was independent of diabetes, insulin resistance, or the metabolic syndrome (Liangpunsakul and Chalasani, 2005). In a survey of a nationally representative sample of the US civilian non-institutionalized population (N = 15,029), Tsui et al. (2006) noted an age-dependent association between HCV seropositive rate and albuminuria (adjusted OR and 95% CI 0.83, 0.30–1.75 for ages 20–39; 1.84, 1.00–3.37 for ages 40–59; 2.47, 1.27–4.80 for ≥ 60 years respectively). Albuminuria was determined on the basis of spot urine albumin:creatinine ratios. One possible explanation of the age-dependent association between HCV and proteinuria could be the time-dependent development nature of renal disease.

Recently, Fischer et al. (2010) evaluated a national cohort (N = 23,155) of HIV-infected veterans in the United States. They observed a graduated increase in prevalence of HCV co-infection with worsening eGFR, ranging from 39% in those with normal kidney function to 60% in those with eGFR < 15 mL/min (P < 0.05). Noureddine et al. (2010) retrospectively identified patients (N = 111) with primary GN on biopsy. By Cox regression analysis, hepatitis C-seropositive patients had a more rapid decline in kidney function than those who were negative, HR 0.46 (95% CI 0.27–0.88; P < 0.001) or not tested, HR 0.11 (95% CI 0.03–0.34; P < 0.001). These findings might explain why the absence of an overall association of hepatitis C with uraemia in some surveys (Tsui et al., 2006; Moe et al., 2008). If the detrimental effect of hepatitis C is primarily on the progression of glomerular disease, then mixed cohorts of both non-glomerular and glomerular diseases may fail to find a relationship. It is biologically plausible that HCV may principally

impact glomerular disease more, as HCV antigens have been isolated in glomeruli and tubules on kidney biopsies (Sansonno et al., 1997, 2005). Immune complexes and viral particles have been noted in the glomerular capillary subendothelium and mesangium.

Hepatitis C virus-related nephropathy: pathogenesis

A number of glomerular and tubulointerstitial patterns of injury (Kasuno et al., 2003) have been described in association with HCV, however, the causal role of HCV is not clearly established in a majority of these. GN develops many years, even decades, after initial infection. Why only some HCV-infected patients develop kidney lesions has not been explained.

The most common HCV-related nephropathy is type I MPGN, usually in the context of type II cryoglobulinaemia. Less frequently described lesions are MPGN without cryoglobulinaemia, membranous nephropathy (Stehman-Breen et al., 1995), immunoglobulin (Ig)-A nephropathy, acute diffuse proliferative GN, focal segmental glomerulosclerosis (Stehman-Breen et al., 1999), thrombotic microangiopathy (Baid et al., 1999), and fibrillary or immunotactoid glomerulopathy (Markowitz et al., 1998). In addition, vasculitis and interstitial nephritis have been associated with HCV. The natural history of these HCV-associated nephropathies is characterized by remissions and relapses; the long-term outcome, however, is not well known.

The presence of cryoglobulins and HCV antigen–antibody complexes have been implicated in the pathogenesis of HCV-induced nephropathy. Barsoum (2007) suggested that the renal microstructure is suited for sieving macromolecules associated with HCV such as cryoglobulins and immune complexes containing viral antigens and antibodies. However, they cannot explain all renal lesions associated with HCV infection. A proportion of HCV-infected patients show pathologic changes in the kidney without evidence of immune-mediated injury. This is particularly evident in the setting of kidney or liver transplantation. An alternative explanation for the renal lesions is the cytopathic effect of HCV. Renal parenchyma expresses glycosaminoglycans, toll-like receptors (Wornle et al., 2006). and low-density lipoproteins which are useful for attachment, entry, and endocytosis of HCV in the kidney, respectively. The replication of HCV in the kidney by infection of B-lymphocytes has been also suggested.

Hepatitis C virus-associated cryoglobulinaemic glomerulonephritis: clinical manifestations

Mixed cryoglobulinaemia (MC) with type I MPGN is the commonest renal lesion described with HCV infection. Since the identification of hepatitis C virus (Choo et al., 1989), it has been discovered that almost all cases of MC are related to chronic HCV infection.

Patients with HCV-related cryoglobulinaemic GN can present with nephritic syndrome, asymptomatic non-nephrotic proteinuria or haematuria, and/or reduced GFR. Acute nephritic and nephrotic syndrome can be a presenting feature in 25% and 20% of the patients, respectively. Cryoglobulins and HCV RNA are usually present, hypocomplementaemia and positive rheumatoid factor can also be observed. In non-cryoglobulinaemic MPGN, the clinical picture, histologic features, and laboratory data are indistinguishable from idiopathic type I MPGN.

The clinical course of MC is characterized by periods of exacerbation of the extrarenal symptoms alternating with periods of quiescence. Extrarenal flares may be associated with exacerbations of the renal disease. In most cases, the exacerbation or remission of the renal disease can occur independent of the course of the systemic disease, or the renal disease shows an indolent course. End-stage renal disease requiring dialysis is relatively infrequent even many years after the onset of cryoglobulinaemic GN. Of 105 patients with cryoglobulinaemic nephritis followed-up for a median period of 131 months, 42 died of cardiovascular disease, infection, and neoplasia (Tarantino et al., 1995). On multivariate analysis, old age, vascular purpura, splenomegaly, raised serum creatinine at the time of kidney biopsy, high cryocrit, and low C3 values were independently associated with death or renal failure.

Hepatitis C virus-associated cryoglobulinaemic glomerulonephritis: histology

The most frequent histologic picture of cryoglobulinaemic GN is that of MPGN. Distinctive features of cryoglobulinaemic GN, especially in patients with rapidly progressive deterioration of renal function, include intraglomerular deposits, commonly observed in a subendothelial location, which might fill the capillary lumen (intraluminal thrombi). These are large eosinophilic, periodic acid–Schiff (PAS)-positive amorphous deposits. On electron microscopy, they exhibit a fibrillary or cylindric structure, 100 to 1000 nm in diameter, identical to that seen in *in vitro* cryoprecipitates. The circulating monoclonal IgM rheumatoid factor is of the same idiotype as that seen in the biopsy specimens supporting the circulatory origin of the intraglomerular (subendothelial and intraluminal) deposits with the circulating IgG-IgMk cryoglobulins.

An important feature of cryoglobulinaemic GN is the glomerular hypercellularity, secondary to an influx of leucocytes (mainly monocytes). The number of infiltrating leucocytes is higher in cryoglobulinaemic GN than in severe proliferative lupus nephritis. These leucocytes have intracytoplasmatic deposits and are in close contact with the endocapillary and subendothelial deposits.

The double-contouring of the glomerular basement membrane is apparent in the acute stages of the disease and is more diffuse than in lupus nephritis and in idiopathic MPGN. Ultrastructural analysis shows that peripheral interposition of the mesangial cells and mesangial matrix and the newly formed basement-membrane-like material is less evident than in idiopathic MPGN and in lupus nephritis. Numerous monocytes in close contact with the subendothelial deposits are interposed peripherally to give the double-contoured appearance of the capillary wall. In later stages, as the infiltration lowers, the double-contoured appearance can be less evident.

About 20% of patients with MCs show type-I lobular MPGN with clear centrilobular mesangial sclerosis. They can be distinguished from idiopathic type I MPGN by the prominent infiltration of monocytes. Some patients show mild mesangial proliferative GN with moderate or absent leucocyte infiltration. Acute renal vasculitis, involving small- and medium-sized renal arteries and characterized by fibrinoid necrosis of the arteriolar wall and monocyte infiltration in and around the wall occurs in one-third

of cryoglobulinaemic GN. Vasculitis may occur in the absence of glomerular alterations.

Therapy of hepatitis C virus-associated glomerulonephritis

In view of the role of HCV in the pathogenesis of cryoglobulinaemic GN, antiviral therapy has been used to achieve clearance of HCV and ameliorate the renal injury (Misiani et al., 1994). Johnson et al. (1994) were the first investigators to use interferon alpha (IFNα) therapy for HCV-associated GN in 14 patients, mainly with cryoglobulinaemic GN, who achieved significant reduction in proteinuria but no improvement in renal function. The clinical response was associated with disappearance of circulating HCV RNA during treatment. However, relapse of viraemia and renal disease was common after cessation of therapy. Unfortunately, no information was available on sustained virological response (HCV RNA clearance from serum during antiviral therapy which persists at least 6 months after completing treatment) which is now the aim of antiviral therapy of hepatitis C.

The current recommendations on the use of antiviral therapy are based on several anecdotal reports (Gilli et al., 1996; D'Amico et al., 1998; Lopes et al., 2003; Orlent et al., 2005; Lo et al., 2009; Colucci et al., 2011) and small-sized observational studies (Table 186.2), rather than large randomized studies (Mazzaro et al., 2000; Bruchfeld et al., 2003; Rossi et al., 2003; Alric et al., 2004; Saadoun et al., 2006; Garini et al., 2007; Roccatello et al., 2007; Abbas et al., 2008). Initial reports utilized monotherapy with conventional IFN, but the current gold standard is a combined regimen of IFN, especially pegylated (peg)-IFN, and ribavirin. The available information shows positive results in terms of remission of proteinuria, haematuria and improvement of serum creatinine. These changes are usually associated with the disappearance of HCV viraemia and a decrease in circulating cryoglobulin levels. However, as the HCV eradication is not universal, the clinical benefit may be transient and restricted to patients with low-grade disease. The impact of antiviral therapy on long-term outcomes of kidney disease is not well known. Furthermore, there is dissociation between the antiviral and renal responses; viral clearance can be slow, whereas rapid renal improvement is not uncommon. IFN has been reported to exacerbate proteinuria in some patients with glomerulopathies (Ohta et al., 1999). Ribavirin use is fraught with the risk of worsening of anaemia in patients with CKD. Low-dose treatment is recommended in patients with a creatinine clearance < 50 mL/min/1.73m^2 (Carrion et al., 2011). Among patients with CKD stage 5, 200 mg/daily or 200–400 micrograms three times a week are recommended.

In patients with severe renal disease, antiviral therapy suppresses viraemia and cryoglobulinaemia, but is not fully effective in controlling renal and systemic disease secondary to cryoglobulin deposition. Steroid pulses and cytotoxic agents, with or without plasma exchange, can be useful but can be associated with life-threatening complications, such as infection, increased viral replication, and death.

Recent years have seen a number of reports demonstrating the efficacy of rituximab in patients in whom antiviral therapy is not effective, contraindicated, or not tolerated. Rituximab targets and depletes B-cell clones that sustain the production of pathogenetic cryoglobulins. Only a few uncontrolled studies of HCV-related cryoglobulinaemic GN patients treated with rituximab have been published. Preliminary results are encouraging and some authors have recommended its preferential use in spite of the absence of controlled trials (Quartuccio et al., 2006). In the series by Roccatello et al. (2008), 11 patients with severe MC and HCV infection were included, seven having renal involvement (six with biopsy-proven MPGN). The patients received rituximab therapy at a dose of 375 mg/m^2 on days 1, 8, 15, and 22. Levels of proteinuria and rheumatoid factor decreased significantly ($P < 0.01$), whereas C4 values significantly increased at 2 and 6 months ($P < 0.05$). No acute or delayed side effects were shown. However, a point of caution is important, as rituximab use has been associated with severe infectious complications including reactivation of HCV (Perceau et al., 2006). This could have implications for patients with other immunosuppressive conditions such as cirrhosis and renal failure. We reported on a renal transplant recipient with chronic hepatitis C who received standard rituximab therapy for gastric lymphoma (Fabrizi et al., 2007). Rituximab use was complicated by cholestatic hepatitis C with extremely high HCV RNA titres (> 7,692,310 IU/L); liver insufficiency occurred. Although other mechanisms could not be excluded, we implicated rituximab in the pathogenesis of cholestatic hepatitis C in our patient.

Recently, two randomized controlled trials (RCTs) evaluating the efficacy and safety of rituximab therapy for cryoglobulinaemic vasculitis have been reported. Rituximab therapy was shown in both the studies to be superior to conventional immunosuppressive drugs for treating cryoglobulinaemic vasculitis, providing further evidence of its clinical efficacy and safety in this setting. In the first trial, De Vita and co-workers (2012) compared rituximab (1 g intravenously days 0 and 14) with conventional therapy (corticosteroids, plasma exchange, azathioprine, or cyclophosphamide) in 57 patients with severe cryoglobulinaemic vasculitis. HCV infection was noted in 53 out of 57 patients. The trial was stopped early, after an interim analysis showing that the proportion of patients who continued to take their initial therapy at 12 months was greater in the rituximab compared with the conventional therapy arm (64.3% vs 3.5%; $P < 0.0001$). Among the seven patients in the rituximab arm who had GN, five showed a complete or partial response; no detailed information was given on this point in the conventional therapy group. Sneller and colleagues (2012) randomized 24 patients with HCV-related cryoglobulinaemic vasculitis to receive a weekly infusion of rituximab for 4 weeks or standard

Table 186.2 Antiviral treatment of HCV-associated GN: recent clinical trials

Authors	Sustained virological response	Country	Reference year
Mazzaro et al.	14% (1/7)	Italy	2000
Bruchfeld et al.	71% (5/7)	Sweden	2003
Rossi et al.	100% (3/3)	Italy	2003
Alric et al.	67% (12/18)	France	2004
Saadoun et al.	59% (13/22)	France	2006
Roccatello et al.	11% (6/55)	Italy	2007
Garini et al.	75% (3/4)	Italy	2007
Abbas et al.	13% (4/30)	Pakistan	2008

therapy (maintained or intensified conventional immunosuppressive therapy). Clinical remission at 6 months was more common in the rituximab arm compared to conventional immunosuppressive therapy (83.3% vs 8.3%; P < 0.001). Of the four patients with GN in the control group, all experienced a decline in the estimated GFR over the 6-month study period. In contrast, all four patients in the rituximab group either maintained stable renal function or had improvement in the estimated GFR. Based on the results of these clinical trials, rituximab may be an option for severe HCV-associated cryoglobulinaemic vasculitis.

Recently, some authors suggested rituximab followed by peg-IFNα/ribavirin in HCV-related MC in order to target either the viral trigger (HCV) and the downstream B-cell clonal expansion (Dammacco et al., 2010). Saadoun et al. (2010) prospectively compared the combination of rituximab plus peg-IFNα/ribavirin (n = 38) versus peg-IFNα/ribavirin (n = 55) in HCV-related MC. The overall SVR rate was 59.1% (55/93) with no difference between the two groups. In the subgroup of patients with kidney involvement (n = 31), complete remission of kidney abnormalities was more common in patients treated with rituximab plus peg-IFNα/ribavirin compared with those receiving peg-IFNα/ribavirin, 80.9% (17/21) vs 40% (4/10), P = 0.040. At the end of follow-up, proteinuria decrease was larger in the first than in the second group, 3.5 ± 0.9/0.35 ± 0.1 (P = 0.001) and 3.1 ± 0.9/1.2 ± 0.5 (P = 0.04), respectively. Improvement in serum creatinine, 217.5 ± 47.4/136.9 ± 27.1 μmol/L (P = 0.03) and GFR, 42.8 ± 5.8/57.6 ± 4.5 mL/min (P = 0.01) at the end of follow-up was noted only in the first group. Information on the SVR rate in this subset of patients was not given. Rituximab plus peg-IFNα therapy was well tolerated. The conclusion of the authors was that rituximab synergizes the immunologic effects of antiviral therapy; rituximab plus antiviral agents may be a good option for treating HCV-infected patients with severe cryoglobulinaemic vasculitis, provided no new safety concerns are raised using this approach.

Data are lacking on efficacy and safety of triple antiviral therapy in HCV-induced MC. Saadoun et al. (2014) showed that triple antiviral therapy (i.e. peg-IFNα/ribavirin/protease inhibitor combination) improved the rates of viral and clinical response in patients with HCV-associated MC vasculitis; the HCV RNA clearance was 69.6% at week 24 with complete response in 56.5%. However, grades 3 and 4 adverse events (mainly anaemia, neutropenia, and thrombocytopenia) were found in 43.5% of patients. All six patients with HCV-related MC and kidney involvement showed improvement in kidney disease, although two out of six also received rituximab. Long-term follow-up is warranted to further analyse the safety and efficacy of the peg-IFNα/ribavirin/protease inhibitor combination in HCV-induced MC vasculitis. Studies in patients with HCV-related GN are under way.

Deciding on the treatment is a complex issue that should take into account variables like patient age, likelihood of response, and co-morbidities that may decrease life expectancy or contraindicate the use of immunosuppressive or antiviral agents. It is clear that prospective, multicentre RCTs are needed to establish evidence-based recommendations to treat glomerular lesions associated with HCV infection. However, until this information is available, two possible regimens should be considered for the treatment of cryoglobulinaemic GN, depending on the severity of proteinuria and kidney failure (Table 186.3). Finally, in all cases, treatment including diuretics and antihypertensive agents should be used to achieve recommended target blood pressure goals of patients with CKD. Antiproteinuric agents such as angiotensin-converting enzyme inhibitors alone or in combination with angiotensin receptor blockers should be used to maximally reduce urinary protein losses.

Table 186.3 Therapy of HCV-associated nephropathy

Moderate proteinuria and/or slow kidney failure	Antiviral therapy (rIFN or peg-IFN plus ribavirin), 12 months
	rIFN (3 MUI) ×3/week SC
	Peg-IFNα-2a 180 mcg/kg per week SC (or 135 mcg/kg per week SC in patients with reduced creatinine clearance)
	Peg-IFNα-2b 1.5 mcg/kg per week SC (or 1.0 mcg/kg per week SC in patients with reduced creatinine clearance)
	Ribavirin 10–15 mg/kg per day, orally (or 400 mg ×3/week in patients with GFR < 15 mL/min)
	EPO (IV/SC) according to HB value
	Symptomatic therapy: furosemide, ACEI and/or ARB
Nephrotic range proteinuria and/or rapidly progressive kidney failure and/or acute flare of cryoglobulinaemia	Step I: corticosteroid therapy: IV MP boluses (1.0–0.5/day on 3 consecutive days) plus oral CCS (0.5 mg/kg per day slowly tapered to 0.1–0.2 mg/kg per day, 4–6 months)
	Oral cyclophosphamide (1–2 mg/kg per day, 2–4 months)
	Plasma exchange (exchanges of 2–3 L plasma ×3/week, 2–3 weeks)
	Rituximab IV (375 mg/m^2 per week, 4 weeks)
	Step II: antiviral therapy (as shown above)
	Symptomatic therapy (as above)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCS = corticosteroid; EPO = recombinant human erythropoietin; HB = haemoglobin; IV = intravenously; mcg = micrograms; MP = methylprednisolone; peg-IFN = pegylated interferon; rIFN = recombinant interferon; SC = subcutaneously.

Hepatitis C virus-associated glomerulonephritis after transplantation

The exact prevalence of HCV-related GN after liver or renal transplant is probably low even if the information on this point is scarce. HCV-infected renal as well as liver allograft recipients are prone to develop immune complex-mediated GN as it occurs in non-transplanted setting. The estimated prevalence of glomerular lesions in HCV renal allografts varies depending on evaluating protocol or criteria for kidney biopsy; nevertheless, estimated prevalence is 5–15% (Cruzado et al., 2001). The most frequent GN associated with HCV after renal transplantation is MPGN followed by membranous nephropathy, according to reported series (Perico et al., 2009). *De novo* or recurrent GN associated with HCV occurs at the early stage of kidney transplant (from 30 days to 10 months). More limited information exists on HCV-associated GN after liver transplantation. Abrahamian et al. (2000) found four (13%) patients with HCV-associated GN among 31 HCV-positive liver transplant recipients. Antiviral therapy which remains the cornerstone of

treatment for HCV-induced cryoglobulinaemic GN is not indicated after renal transplantation because of several reports of early steroid-resistant rejection; this being attributed to the immunomodulatory properties of IFN. Only anecdotal experience has been reported on the use of IFN-based therapy for HCV-induced symptomatic MC and/or HCV-associated glomerular disease after liver or liver/kidney transplant (Sikaneta et al., 2002; Montalbano et al., 2007; Donato et al., 2013). Antiviral therapy can lead to a sustained viral clearance associated with remission of cryoglobulinaemic complications (including reduction of proteinuria and improvement of GFR). A small number of cases have reported the benefit of ribavirin monotherapy on HCV-related glomerular disease. According to the study of Hu and Jaber (2005), a patient with refractory nephrotic syndrome secondary to HCV-related membranous nephropathy had a complete recovery following the initiation of ribavirin monotherapy.

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CHAPTER 187

HIV and renal disease

Saraladevi Naicker and Graham Paget

Introduction

The World Health Organization's (WHO's) Global Health Observatory in 2013 estimated that there are 35 (33.2–37.2) million people living worldwide with human immunodeficiency virus (HIV) infection, with approximately 39 million deaths due to AIDS, of the 78 million estimated to have been infected (WHO, 2013). HIV infection is a continuing crisis that particularly affects the poorer regions of the world, with 71% of people with HIV infection living in Sub Saharan Africa (WHO, 2013). The availability of antiretroviral therapy (ART) has resulted in improved survival and increasing numbers of patients with renal disease requiring therapy.

Patterns of renal disease associated with HIV infection

HIV can affect the kidney either directly or indirectly. Patterns of HIV-associated kidney disease vary, depending on the socioeconomic and demographic characteristics of the population concerned, as well as exposure of patients to antiretroviral agents. Table 187.1 summarizes aspects of kidney disease with HIV infection and Table 187.2 the glomerular lesions found in HIV infection.

Epidemiology of chronic kidney disease with HIV infection

There is increasing evidence of a high prevalence of chronic kidney disease (CKD) in people infected with HIV. The prevalence was reported as 15.5% in an urban population in the United States (Wyatt et al., 2007). In a cross-sectional study from 31 European countries, Israel, and Argentina (Eurosida Study Group), CKD (defined as an estimated glomerular filtration rate (eGFR) of ≤ 60 mL/min/1.73 m^2) was present in 3.5–4.5% of individuals with HIV infection (Mocroft et al., 2007). A study from Hong Kong reported CKD (defined as eGFR ≤ 60 mL/min/1.73 m^2 and/or proteinuria for > 3 months) in 16.8% of HIV-infected Chinese patients (Cheung et al., 2007). Importantly, this study excluded those with end-stage renal disease (ESRD). Isolated screening studies with relatively small numbers using persistent proteinuria as a marker of CKD have shown the following prevalence rates: 5.6% in Brazil (Cavalcante et al., 2007), 27% in India (Janakiraman et al., 2008), and 12.3% in Iran (Ramezani et al., 2008). An autopsy study from Switzerland reported CKD in 18% (Hailemariam et al., 2001). Studies from Africa have reported a variable prevalence of renal disease in HIV: 5.5–6% in South Africa (Han et al., 2006; Fabian et al., 2013), 38% in Nigeria (Emem et al., 2008), 26% in Cote d'Ivoire (Mortier et al., 2003), 11.5% in Kenya (Wools-Kaloustian et al., 2007), 20% in Uganda (Peters et al., 2008), and 33.5% in Zambia (Mulenga et al., 2008) (Tables 187.3 and 187.4). This wide variation may be partly ascribed to differences in study design, the populations studied, and definitions used for CKD. Renal histology was not available in the majority of these reports.

HIV-associated nephropathy (HIVAN) has been reported to occur predominantly in HIV-infected populations of black ethnicity, while immune complex disease occurred in populations of Caucasian, Asian, and Oriental origins (Szczech et al., 2004). People of African descent are at > 18-fold-increased risk for developing HIVAN compared with people of European descent (Kopp et al., 2008). Table 187.5 reports the histological patterns seen in South Africa and Nigeria, where the HIV-infected populations studied were predominantly of black African origin. While HIVAN predominated in the studies reported from Durban (Han et al., 2006), Cape Town (Swanepoel and Okpechi, 2011), and Nigeria (Emem et al., 2008), immune complex disease has been reported to occur in a large proportion of black African patients from Johannesburg (Gerntholtz et al., 2006; Fabian et al., 2013) and Cape Town (Wearne et al., 2012).

Acute kidney injury in HIV infection

The frequency of acute kidney injury (AKI) in patients admitted with HIV infection to hospital in Lisbon, Portugal from 2005 to 2007 was 18%. The commonest aetiologies of AKI were sepsis (59%), nephrotoxic drug administration (37.5%), volume depletion (21.6%), and radiocontrast use (20.5%) (Lopes et al., 2011).

Pathogenesis of HIV-associated nephropathy

The protean manifestations of CKD in patients with HIV infection are the result of a complex interplay between the pheno- and/or genotypic variants of HIV, the genetic make-up of the host, and environmental factors. HIV infection of the renal epithelium and subsequent expression of viral gene products is a major driver of HIVAN (Bruggeman et al., 2000). The mechanism by which HIV gains entry to cells in the kidney is unclear, as renal epithelial cells do not express the primary HIV receptor, CD4 or its main co-receptors CXCR4 or CCR5. Not all patients with infection of the renal epithelium develop HIVAN, suggesting that host responses also determine whether the infection will lead to HIVAN. The viral genes *nef* and *vpr* increase podocyte proliferation and dedifferentiation (He et al., 2004; Husain et al., 2005; Zuo et al., 2006). A number of inflammatory cytokines such as transforming growth

Table 187.1 Patterns of renal disease with HIV infection

Direct renal effects associated with HIV infection		
Acute kidney injury	**Chronic kidney disease**	**Electrolyte and acid–base disorders**
Prerenal causes associated with dehydration (e.g. gastroenteritis, pancreatitis)	HIV-associated nephropathy (HIVAN)	Hyponatraemia related to syndrome of inappropriate antidiuretic hormone secretion, volume depletion, and adrenal insufficiency (Glassock et al., 1990)
Infections, septic shock	HIV immune complex glomerulonephritis	Hypernatraemia related to dehydration
Myocardial dysfunction (e.g. cardiomyopathy)		Hyperkalaemia related to renal dysfunction, trimethoprim, or IVI pentamidine use and adrenal insufficiency (Berns et al., 1991)
Liver failure (HIV cholangiopathy or co-infection with hepatitis B and/or C with hepatorenal syndrome)		Hypokalaemia related to diarrhoeal illness and the use of amphotericin B
		Metabolic acidosis related to type A lactic acidosis from tissue hypoperfusion and type B lactic acidosis related to stavudine use or liver disease or kidney failure (Chattha, et al., 1993)
Indirect renal effects associated with HIV infection		
Acute kidney injury	**Chronic kidney disease**	
Toxins, especially traditional herbal medications	Metabolic syndrome (diabetes mellitus and hypertension) associated with antiretroviral therapy use	
Analgesics, especially non-steroidal anti-inflammatory drugs	Other chronic kidney diseases with incidental HIV infection (which may exacerbate progression of CKD)	
Antiretroviral agents, especially tenofovir (tubular toxicity), ritonavir (exacerbates tenofovir nephrotoxicity) (Fernandez-Fernanadez et al., 2011), indinavir (crystal formation and obstruction), and stavudine (lactic acidosis and/or pancreatitis) (Berns et al., 1991)		

Table 187.2 Spectrum of glomerular lesions in HIV infection

Glomerular pattern	**Subtypes**
HIV-FSGS (focal segmental glomerulosclerosis) or 'classic' HIVAN (HIV-associated nephropathy; FSGS with collapsing glomerulopathy)	Some have described a mixed variant of HIV-FSGS in combination with a proliferative glomerulonephritis
HIV-ICD (HIV-immune complex disease) (this group may have co-infection with hepatitis B or C)	Mesangial proliferative Membranoproliferative (type I and III) Lupus-like Exudative-proliferative Crescentic Immunoglobulin A Membranous
Various glomerulonephropathies (this is a heterogeneous group with different aetiologies)	Minimal change Immunotactoid Amyloidosis
HIV-TTP/HUS	Thrombotic thrombocytopenic purpura Haemolytic uraemic syndrome

Table 187.3 Prevalence of HIV CKD globally

Country	**Method of screening**	**Population characteristics**	**Prevalence (%)**
United States[1]	Proteinuria; eGFR	1239 HIV+/M704; F535/ CD4 396 ± 314	15.5
Europe & Israel, Argentina (Eurosida)[2]	eGFR	4474 HIV+/M3404; F1070/ CD4 455 (310–645)	3.5–4.5
Hong Kong[3]	Proteinuria; eGFR	322 HIV+/M264; F58/CD4 102 ± 117	16.8
Brazil[4]	Proteinuria	411 HIV+/M287; F124/CD4 363 ± 95	5.6
Switzerland[5]	Autopsy study	239HIV+/M195; F44	18
India[6]	Proteinuria	104 HIV+/M68; F36/CD4 310 ± 297	27
Iran[7]	Proteinuria	171 HIV+/M138; F33/CD4 333 ± 196	12.3

F = female; M = male.

[1] Wyatt et al. (2007).

[2] Mocroft et al. (2007).

[3] Cheung et al. (2007).

[4] Cavalcante et al. (2007)

[5] Hailemariam et al. (2001).

[6] Janakiraman et al. (2008).

[7] Ramezani et al. (2008).

factor beta (TGF-β), interleukin (IL)-6, IL-8, tumour necrosis factor alpha (TNF-α) and monocyte chemoattractant protein-1 (MCP-1) are produced in response to podocyte and tubular epithelial cell infection by HIV and regulated by nuclear factor kappa B (NF-κB) (O'Donnell et al., 1998; Bruggeman and Nelson, 2009). Fibroblast growth factor-2 (FGF-2) is upregulated (Liu et al., 2001), and TGF-β has been shown to be overexpressed in the kidneys in HIVAN (Yamamoto et al., 1999).

The expression of podocyte proteins such as synaptopodin, podocalyxin, and Wilms tumour 1(WT-1) is downregulated in HIV

Table 187.4 Prevalence of HIV CKD- Africa

Country	Method of screening	Population characteristics	Prevalence (%)
South Africa[1, 2]	Proteinuria; eGFR	578 HIV+/M217; F261/ CD4 130 (1–828) 615 HIV+/M139; F431/ CD4 251 (3–641)	5.5–6
Nigeria[3]	Proteinuria; serum creatinine	400 HIV+/M210; F190/ CD4 246 ± 192	38
Cote d'Ivoire[4]	Proteinuria	91 HIV+/M30; F61/ CD4 117	26
Kenya[5]	eGFR	373 HIV+/M109; F264/ CD4 391 (91–1245)	11.5
Uganda[6]	eGFR	508 HIV+/M207; F301/ CD4 122	20
Zambia[7]	eGFR	25799 HIV+	33.5

F = female; M = male.

[1] Fabian et al. (2009).

[2] Han et al. (2006).

[3] Emem et al. (2008).

[4] Mortier et al. (2003).

[5] Wools-Kaloustian et al. (2007).

[6] Peters et al. (2008).

[7] Mulenga et al. (2008).

infection (Barisoni et al., 2000). Podocytes, similar to tubular epithelial cells, undergo a phenotypic conversion after TGF-β stimulation which is upregulated in diseased kidneys. Podocytes proliferate and undergo apoptosis in human HIVAN as well as mouse models, resulting in pseudocrescents and glomerular collapse (Barisoni and Kopp, 2002; Zuo et al., 2006). HIVAN is characterized by enhanced proliferation and the loss of differentiation markers of glomerular epithelial cells, induced by *nef* through activation of Src-dependent Stat and MAPK pathways. Transgenic mice that expressed *nef* in podocytes showed expression of the proliferation marker Ki-67 in podocytes and downregulation of synaptopodin (Husain et al., 2005). These observations suggest that dysregulation of cell cycles or apoptosis may be involved in HIVAN pathogenesis, resulting in glomerulosclerosis and tubulointerstitial disease.

In one study, HIV-1 infection was shown to kill renal tubular epithelial cells *in vitro* by triggering an apoptotic pathway involving caspase activation and fas upregulation. NF-κB regulates apoptosis by controlling the expression of fas ligand (Ross et al., 2005). The combined glomerular and tubular epithelial cell damage leads to proteinuria, glomerulosclerosis, and tubulointerstitial scarring. Viral replication in response to cytokine stimulation may play an important role in the pathogenesis of HIVAN.

Table 187.5 Renal histology in HIV infection in Africa

	JHB[1]	JHB[2]	JHB[3]	DBN[4]	CT[5]	CT[6]	Nigeria[7]
Number of biopsies	99	20	159	37	145	192	10
HIVAN (%)	27	5	22	83	55	57.3	70
IC disease (%)	21	40	17			30.2	
Other GN (%)	41		38.5	7	15.9	12.5	
Tubulo-interstitial disease (%)			3.1	10	13		70
Other (%)	10	35	21.4		16		

CT = Cape Town; DBN = Durban; JHB = Johannesburg.

[1] Gerntholtz et al. (2006).

[2] Fabian et al. (2013).

[3] Diana et al. (2013)

[4] Han et al. (2006).

[5] Swanepoel and Okpechi. (2011).

[6] Wearne et al. (2012).

[7] Emem et al. (2008).

Genetics of HIV-associated kidney disease

HIVAN has a predilection for persons of African ancestry, who exhibit a 20-fold increase in relative risk compared with individuals of Caucasian descent. Approximately 10% of African Americans with HIV-1 infection develop renal disease, suggesting that there are genetic factors which render these individuals susceptible to HIVAN (Kopp et al., 2008).

A transgenic mouse model of HIVAN has allowed identification of loci in the mouse genome associated with HIVAN susceptibility. When the transgenic strain was crossed with other strains, renal disease was modified, suggesting that host genes play an important role in the development of HIVAN. The loci include *HIVAN1*, which corresponds to 3q25–27 in humans. Another locus, *HIVAN2* on mouse chromosome 13 (Bruggeman et al., 1997; Papeta et al., 2009), is critical in regulating levels of podocin expression. The presence of these loci may modulate expression of the *NPHS1* and *-2, SYNPO, KIRREL*, and *MYH9* genes in the presence of HIV infection (Papeta et al., 2009).

In terms of human genetics, the susceptibility for HIVAN was attributed to variants in the *MYH9* gene, encoding myosin heavy chain 9, with an odds ratio of 4 and 6 for idiopathic focal segmental glomerulosclerosis (FSGS) and HIVAN, respectively. *MYH9*, localized on chromosome 22q12 was an attractive candidate gene, as it is expressed in podocytes (Kopp et al., 2008). Later studies showed a closer association of apolipoprotein L1 (*APOL1*) gene variants G1 and G2 (which are in strong linkage disequilibrium with *MYH9*) and FSGS (HIV and non-HIV associated) in people of African descent (Genovese et al., 2010; Kronenberg, 2011). This is discussed further in Chapter 341, and MYH9 in Chapter 342.

APOL1 is involved in autophagy, which protects against podocyte ageing and glomerular injury. It causes lysis of pathogenic *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*, which cause human African trypanosomiasis in East and West Africa, respectively. Both these species have evolved independent mechanisms to avoid lysis by APOL1. It has been shown that harbouring *APOL1* risk variants protects against trypanosomiasis disease. There is evidence attributed to natural selection as a result of the trypanosomiasis endemic in Africa that provided an evolutionary advantage. *APOL1* is primarily responsible for the FSGS association (Hays and Wyatt, 2012; Wyatt, 2012).The functions of these genes in renal cells and how their

polymorphisms predispose to kidney disease has not been fully elucidated (Chapter 341).

Progression of HIV-associated chronic kidney disease

It is important to distinguish progression of true HIV-associated kidney disease from other non-HIV related forms of progressive CKD (either glomerular or tubulointerstitial) that may coincidentally exist in HIV-infected individuals.

The two characteristic forms of HIV nephropathy directly attributed to HIV infection are collapsing FSGS with interstitial inflammation and microcystic tubular dilatation (referred to as 'HIVAN') (Fig. 187.1) and immune complex-mediated glomerulonephritis (referred to as 'HIVICD'). Progression of HIVAN has not been fully elucidated, but epithelial to mesenchymal transition of renal epithelial and tubular cells as well as the mammalian target of rapamycin pathway has been demonstrated to be important in mouse models of HIVAN. HIVICD tends to behave similarly to other immune complex-mediated glomerulonephropathies, and is the predominant form of HIV nephropathy in non-black populations (Estrella et al., 2010).

Repeated episodes of AKI affect the progression of CKD in patients with HIV infection. Rise in serum creatinine in hospital of > 0.3 mg/dL (26.4 μmol/L) or 150% above baseline conferred a 1.37-fold increased risk of progression to ESRD in hospitalized HIV-infected individuals (Choi et al., 2010).

The extent of chronic kidney damage at biopsy has been suggested to be the main predictor of progression of kidney disease in HIVAN, and not the use of highly active ART or the achievement of viral suppression in plasma (Post et al., 2008). In this study, 61 patients with HIVAN were followed from 1998 to 2004. After a median follow-up of 4.2 years, 56% of patients had developed ESRD. There were no significant differences in kidney function, viral load, or CD4 counts at enrolment and time to initiation of therapy or the levels of viral suppression achieved between progressors and non-progressors. Only the index of chronic damage score on biopsy predicted renal survival. These data are supported by a study from France that concluded that predictors of progression were renal dysfunction at time of diagnosis, percentage of sclerotic glomeruli (> 30%), time from HIV infection to HIVAN diagnosis of > 1 year, prior exposure to ART, and the use of renin–angiotensin system (RAS) blockers. There was a trend towards better renal outcome associated with viral suppression during follow-up (Bigé et al., 2012).

Most of the work on the role of steroids and the use of RAS blockade in prevention of progression to ESRD is from the pre-ART era. (Kimmel et al., 1996; Burns et al., 1997; Eustace et al., 2000; Winston et al., 2000; Sothinathan et al., 2001). Their role in combination with ART has not been established. Table 187.6 summarizes these studies.

A number of studies have shown a role for ART in preventing progression of HIVAN. One study mathematically modelled renal disease progression and predicted a beneficial role of ART in slowing down disease progression (Schwartz et al., 2005). Szczech et al. found that progression of renal disease mirrored increasing viral RNA levels and hypothesized that reducing RNA levels with ART should have a beneficial effect (Szczech et al., 2002). Kimmel et al. reviewed two case reports of resolution of clinical and pathological features of HIVAN with ART use (Kimmel et al., 2003). Kirchner reported on three patients believed to have HIVAN, whose renal function improved after treatment with a regimen comprising two nucleoside reverse transcriptase inhibitors and a protease inhibitor (Kirchner, 2002). The prevalence of HIVAN has decreased since the advent of ART. There are no prospective trials of significance looking at the role of ART in delaying progression of HIVAN at different stages of disease.

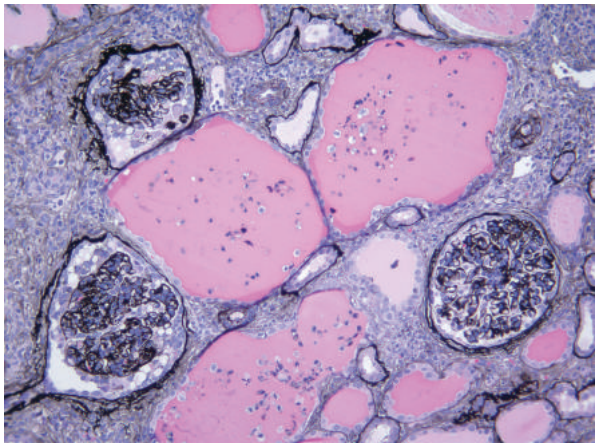

Fig. 187.1 Histology of HIV-associated nephropathy showing glomerular collapse with a focal sclerosing lesion, microcystic tubular dilatation, and interstitial inflammation (magnification ×200)
Courtesy of Professor Stewart Goetsch, University of the Witwatersrand.

Table 187.6 Studies on use of corticosteroids and renin angiotensin blockade in HIV chronic kidney disease

Reference (year/therapy)	Type of study	Numbers (N) and results
Sothinathan et al. (2001/steroids)	Case study	N = 1; 2-year creatinine stable but increasing proteinuria
Winston et al. (2000/steroids)	Review	Steroids confer short-term benefits. ACEI stabilize renal function when given with GFR < 2 mg/dL
Eustace et al. (2000/steroids)	Retrospective cohort study	N = 21; 13 with steroids, 8 no steroids. At 6 months, 7 of steroid group and 1 of no steroid group dialysis free (P = 0.06)
Kimmel et al. (1996/ACEI)	Prospective non-randomized	N = 18; 9 treated with captopril three times daily and 9 no therapy. Mean renal survival, 156 ± 71 days vs 37 ± 5 days (P < 0.002)
Burns et al. (1997/ACEI)	Prospective non-randomized	N = 20; serum creatinine and 24-hour protein excretion stable for up to 24 weeks in patients with non-nephrotic-range proteinuria and for up to 12 weeks in patients with nephrotic-range proteinuria when initial serum creatinine is < 2.0 mg/dL

ACEI = angiotensin converting enzyme inhibitor; GFR = glomerular filtration rate.

Other risk factors also impact on the progression of HIVAN. An important risk factor in progression of disease is co-infection with hepatitis C. The impact of hepatitis C depends on its geographic prevalence, particularly related to unsafe blood transfusion practices and intravenous drug use. The risk of progression to CKD is doubled in HIV-positive patients with circulating hepatitis C antibodies (Wyatt et al., 2008). Survivors on ART are also likely to develop diseases of ageing like type 2 diabetes mellitus, dyslipidaemia, and hypertension, which are all associated with CKD progression. Cigarette smoking is also a factor associated with progression of CKD (Orth and Hallan, 2008). It is also now known that ART therapy itself is a risk factor for the development of the metabolic syndrome which might affect the progression of CKD (Jevtović et al., 2009).

Renal replacement therapy

With the increasing survival of HIV-infected patients on ART, the magnitude of HIV-associated ESRD will likely increase worldwide, as it has in developed countries. Life expectancy in HIV-infected individuals has increased by 10–20 years in developed countries and many of these patients are now dying from the complications of ESRD rather than HIV infection. Currently, HIV-infected subjects requiring either haemodialysis or peritoneal dialysis who are stable on ART, are achieving survival rates comparable to those of dialysis patients without HIV infection. The choice of dialysis modality does not impact the survival. The risk factors for mortality in the HIV-infected patients who are on dialysis are a lower CD4 count, a higher viral load, the absence of combination ART, and a history of opportunistic infections (Ahuja et al., 2003; Soleymanian et al., 2006).

Special issues in renal replacement therapy in HIV-infected patients

Haemodialysis

As in the general dialysis population, native arteriovenous fistulae are the preferred types of vascular access because of excellent patency and lower complication rates compared with those associated with other access options (Curi et al., 1999). HIV-infected patients do not have to be isolated from other patients or dialysed on separate machines. Strict use of universal precautions is the best form of prevention of HIV transmission in dialysis units. The risk of HIV seroconversion after a needle stick injury from an infected patient is estimated to be about 0.3% (Wall et al., 1999). Reprocessing dialysers from HIV-positive patients does not increase the risk of transmission to staff members if necessary sterile precautions are undertaken.

Peritoneal dialysis

HIV survives in peritoneal effluents at room temperature for up to 7 days and in peritoneal dialysis exchange tubings for up to 48 hours. Dialysate should therefore be handled as a contaminated body fluid (Farzadegan et al., 1996). Both sodium hypochlorite 50% and household bleach 10% solutions, in dilutions of 1:512, are effective in killing HIV in dialysate. Peritoneal dialysis patients should be instructed to pour dialysate into the home toilet and to dispose of dialysate bags and lines by tying them in plastic bags and disposing of the plastic bags in conventional home waste (Gupta et al., 2005).

Kidney transplantation

Kidney transplantation has been performed with success in HIV-infected patients. Data on liver, kidney, and heart transplant recipients suggest that patient survival rates are similar to those in HIV-uninfected transplant recipients and there has been no increase in the prevalence of opportunistic infections (Roland and Stock, 2003). In a series of 150 kidney transplants performed between 2003 and 2009, Stock et al. (2010) reported patient survival of 94.6% and 88.2% and graft survival 90.4% and 73.7% at 1 year and 3 years, respectively. In spite of high rates of acute rejection (31% and 41% at 1 year and 3 years respectively), graft survival was similar to HIV-uninfected recipients. In areas with high endemic rates of HIV infection, it has been proposed that HIV-infected deceased donor organs may be transplanted into HIV-infected recipients with ESRD (Venter et al., 2008). Four such transplants have been reported with good graft and recipient survival (Muller et al., 2010). After the initial report, a further 20 transplants have been carried out from HIV-positive deceased donors; 1- and 4-year outcomes have shown graft survival at 88% and 83% and patient survival at 94% and 89% respectively (E. Muller, personal communication).

Nephrotoxicity of ART

ART may be associated with the development of the metabolic syndrome and subsequent risk of diabetic and hypertensive kidney diseases (Jevtović et al., 2009). Some drugs used in ART regimens are potentially nephrotoxic. The most important of these is tenofovir fumarate, which has become first-line treatment at initiation of ART. Accumulation of tenofovir in proximal tubular cells is associated with tubular injury, most commonly manifesting as Fanconi syndrome. About 20–30% of the drug is actively transported into the proximal tubular cells by organic ion transporters (predominantly OAT1 and OAT3), and secreted into the tubular lumen via apical membrane transporters MRP4 and MRP2 (multidrug resistance proteins, encoded by the *ABCC4* and *ABCC2* genes). Drugs like probenecid and non-steroidal anti-inflammatory drugs (NSAIDs) reduce entry of tenofovir into tubular cells. Drugs like aciclovir increase serum levels of tenofovir. MRP4 is inhibited by drugs such as probenecid, dipyridamole, NSAIDs, aciclovir, cidofovir, valaciclovir, ganciclovir, and valganciclovir and may enhance tenofovir nephrotoxicity. MRP2 is inhibited by ritonavir, a protease inhibitor which may be co-administered with tenofovir (Fernandez-Fernandez et al., 2011). The mechanism of tubular injury is through mitochondrial toxicity (Herlitz et al., 2010). Phosphate wasting is an important clue to tenofovir nephrotoxicity (Herlitz et al., 2010). The drug has been associated with AKI, with a risk difference of 0.7% reported (Cooper et al., 2010). The impact on longer-term kidney function is controversial as populations and concomitant drugs are diverse. Overall, about 1% of patients exhibit decline in renal function (Jones et al., 2004; Nelson et al., 2007; Bonfanti et al., 2008; Brennan et al., 2011).

Indinavir causes CKD through crystal nephropathy and tubulointerstitial nephritis (Brodie et al., 1998; Marroni et al., 1998). The annual risk of CKD in indinavir users is 11%. Atazanavir is associated with interstitial nephritis. There is a 22% increase in renal dysfunction per year of use; when combined with tenofovir, this figure rose to 41% (Mocroft et al., 2010). The same authors

Table 187.7 Dosing of ART drugs in persons with renal dysfunction (commonly used agents) based on eGFR (MDRD formula)

Drug	eGFR > 60 mL/min	eGFR 30–60 mL/min	eGFR 15–30mL/min	eGFR < 15 mL/min	On dialysis (HD)
NRTIs					
Abacavir (ideally check HLA-B*5701 negative)	300 mg twice daily (usual dose)	300 mg twice daily (usual dose)	300 mg twice daily (usual dose)	300 mg twice daily (usual dose)	No changes/additional doses
Didanosine pt > 60 kg	400 mg once daily	200 mg once daily	125 mg once daily	125 mg once daily	125 mg once daily, no supplemental doses
Didanosine pt < 60 kg	250 mg once daily	125 mg once daily	125 mg once daily	Do not use	75 mg of paediatric solution once daily
Emtricitabine	200 mg once daily	200 mg every 48 hours	200 mg every 72 hours	200 mg every 96 hours	200 mg every 96 hours give after HD
Lamivudine	150 mg 12-hourly or 300 mg once daily	150 mg once daily	100 mg once daily (first dose 150 mg)	25–50 mg once daily (first dose 150 mg)	25 mg every 24 hours after HD
Stavudine pt > 60 kg	40 mg 12 hourly	20 mg 12 hourly	20 mg once daily	20 mg once daily	20 mg once daily after HD
Stavudine pt < 60 kg	30 mg 12 hourly	15 mg 12 hourly	15 mg once daily	15 mg once daily	15 mg once daily after HD
Zidovudine	300 mg 12 hourly	300 mg 12 hourly	300 mg 12 hourly	300 mg once daily	300 mg once daily, after HD
Tenofovir	300 mg once daily	300 mg every 48 hours	300 mg twice weekly	Unknown	300 mg once weekly after a HD session
NNRTIs					
Efavirenz	600 mg at night	600 mg at night	600 mg at night	600 mg at night	No changes/additional doses
Nevirapine	200 mg once daily	200 mg once daily	200 mg once daily	200 mg once daily	200 mg once daily, supplemental dose 200 mg after HD
Etravirine	200 mg twice daily	200 mg twice daily	200 mg twice daily	200 mg twice daily	No changes/additional doses
Delavirdine	400 mg three times a day	400 mg three times a day	400 mg three times a day	400 mg three times a day	No data
Rilpivirine	25mg once a day	25mg once a day	25mg once a day	25mg once a day	25mg once a day
Fixed dose combinations					
Combination		**Standard dose**		**CKD and/or dialysis**	
Atripla® (efavirenz/emtricitabine/tenofovir)		1 tablet at night		Dose adjust individual drugs as above	
Combivir® (zidovudine/lamivudine)		1 tablet twice daily		Dose adjust individual drugs as above	
Epzicom® or Kivexa® (abacavir/lamivudine)		1 tablet daily		Dose adjust individual drugs as above	
Trizivir® (zidovudine/lamivudine/abacavir)		1 tablet twice daily		Dose adjust individual drugs as above	
Truvada® (emtricitabine/tenofovir)		1 tablet daily		GRF > 60 mL/min = 1 tablet daily GFR 30–60 mL/min = 1 tab every 48 hours GFR < 30 mL/min = dose adjust individual drugs as above	
Complera® (rilpivirine/emtricitabine/tenofovir)		1 tablet daily		Dose individual drugs as above	

eGFR = estimated glomerular filtration rate; HD = haemodialysis; HLA = human leucocyte antigen; pt = patient.

noted that after adjustment for traditional factors associated with CKD, cumulative exposure to tenofovir, indinavir, atazanavir, and lopinavir/ritonavir were associated with a significantly increased rate of CKD (annual incidence rate ratio 1.16, 1.12, 1.21, and 1.08, respectively).

Table 187.7 is a recommendation for dosing of ART drugs in people with renal dysfunction (commonly used agents) based on eGFR (Modification of Diet in Renal Disease (MDRD) study formula) (Trullas et al., 2011; McNicholl and Rodriguez, 2012) and fixed dose combinations (McNicholl and Rodriguez, 2011).

Protease inhibitors

These drugs require no dosage adjustments for renal dysfunction. The excipient of amprenavir solution contains propylene glycol and should be avoided in patients with renal dysfunction. It is also important to remember that several of these drugs require boosting with ritonavir to be effective. Unboosted atazanavir should not be used for treatment naïve patients on haemodialysis, and atazanavir should be avoided altogether in patients on haemodialysis. For patients on dialysis, twice daily dosing of lopinavir/ritonavir is recommended, and this combination might not be effective in those with PI resistance.

Fusion inhibitors

The one drug available, enfuvirtide, requires no dosage changes for renal dysfunction.

CCR5 co-receptor antagonists

Maraviroc should not be given to persons with GFR < 30 mL/min who are on CYP3A inhibitors, as this has been associated with postural hypotension and subsequent cardiovascular events.

Integrase inhibitors

No dose changes are necessary for raltegravir.

Screening for chronic kidney disease in HIV infection

According to the Infectious Diseases Society of America guidelines for the management of CKD in HIV infection (Gupta et al., 2005), all individuals should be assessed for kidney disease at the time of diagnosis of HIV infection. This should include a screening urinalysis for proteinuria and haematuria, and estimate of renal function. Those who exhibit proteinuria on initial testing should undergo repeat examination to confirm the presence of *persistent* proteinuria, as false positives are common in patients who may have co-morbid conditions. Any patient with persistent proteinuria, persistent haematuria, or a GFR < 60mL/min/1.73 m^2 should be referred to an institution where a specialist can evaluate this patient. An important caveat is that if no referral system is available, clinicians should initiate ART as early as possible to prevent progression to ESRD (Table 187.8). Considering the resource limitations in many developing countries, it is imperative that screening, early detection, and treatment of HIV-CKD be a public health priority. These recommendations, that all HIV-infected individuals are screened for CKD at presentation and annually thereafter and treated with ART at an early stage (on diagnosis of CKD), need to be widely implemented at all levels of the healthcare system.

Table 187.8 Screening for chronic kidney disease in individuals with HIV infection

High-risk factors	Race: black African ancestry Family history of kidney disease CD4 < 200 cells/mL HIV RNA level > 4000 copies/mL History of nephrotoxic medication Diabetes mellitus Hypertension Hepatitis C virus co-infection
Screening	Urinalysis (for haematuria and proteinuria/albuminuria) Measure kidney function (serum creatinine and estimation of GFR)
Action	Presence of proteinuria/reduced eGFR: • refer to a nephrologist for further investigation • if nephrology referral is not possible, commence ART Absence of proteinuria/reduced eGFR Repeat screening annually

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CHAPTER 188

Hantaviral infections

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Introduction

Hantaviruses are 'emerging' viruses, forming a separate genus in the *Bunyaviridae* family, and the only viral haemorrhagic fever agents with a worldwide distribution, including the temperate Northern hemisphere (Clement et al., 2010). They are enveloped, negative sense single-stranded RNA viruses of the Bunyaviridae family (Schmaljohn and Nichol, 2007; Jonsson et al., 2010), with three segments: S (small, 1.7 kb, encodes the nucleocapsid protein (N), the major viral antigen), M (medium, 3.6kb, encodes a polyprotein cleaved into envelope glycoproteins Gn, formerly G1, and Gc, formerly G2), and L (large, 8.2kb, encodes the L protein functioning as the viral RNA (vRNA)-dependent RNA polymerase (RdRp)). The genomic RNA segments are enclosed separately to complex with the N protein to form helical nucleocapsids which are surrounded by an envelope containing Gn and Gc viral glycoproteins (Muranyi et al., 2005; Schmaljohn and Nichol, 2007; Jonsson et al., 2010). They have an outer lipid layer, meaning they can be inactivated by detergents or a simple bleach solution. To date, 24 distinct species of hantaviruses (Maes et al., 2004, 2009; International Commission on Taxonomy of Viruses, 2012) (Fig. 188.1)—which are not all pathogenic for humans—have been recognized, each carried by their more or less specific rodent reservoir, which also acts as a vector by shedding infectious excreta for a lifetime. Humans are infected mainly by inhalation of aerosolized viral particles from these excreta.

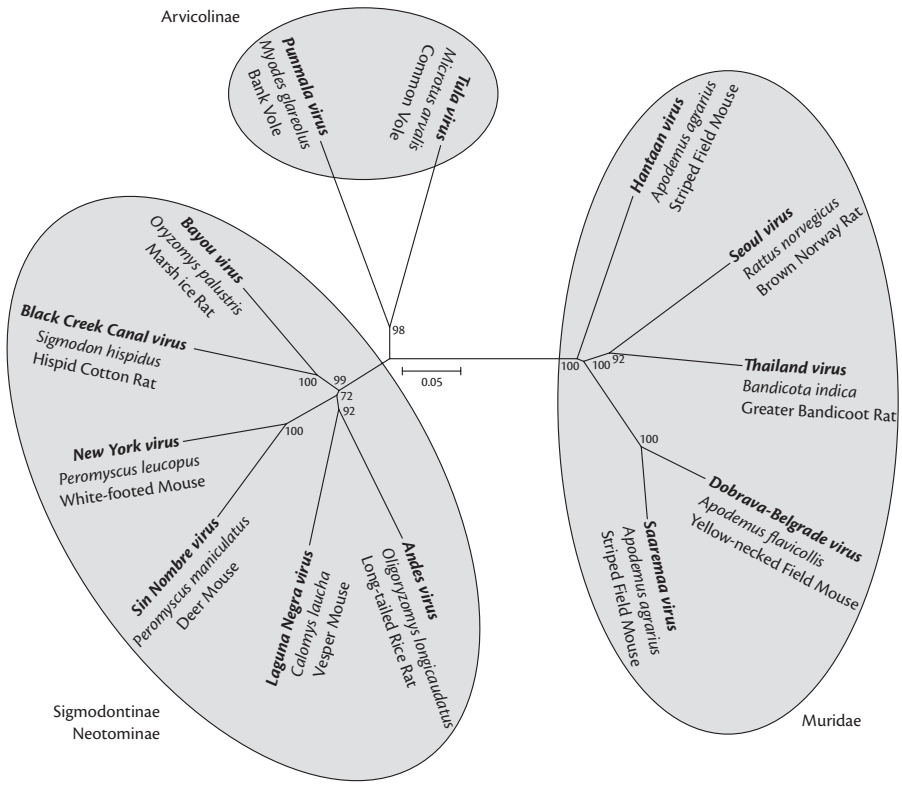
This chapter focuses on the general aspects of hantavirus infections, including the virology, transmission of the disease, new aspects of the epidemiology, and the general pathogenetic mechanisms involved in these infections. Hantavirus-induced acute kidney injury is described in more detail in Chapter 242).

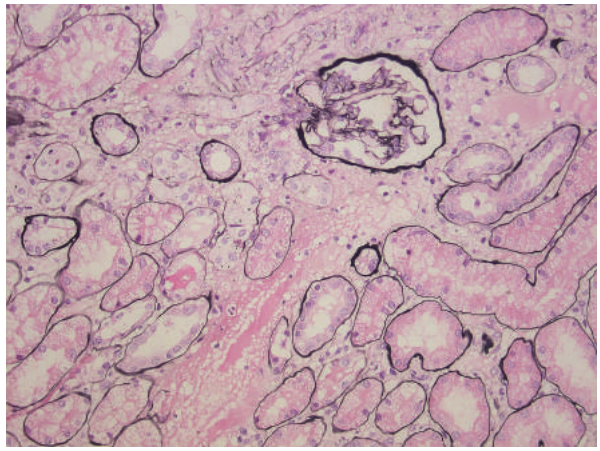
Epidemiology

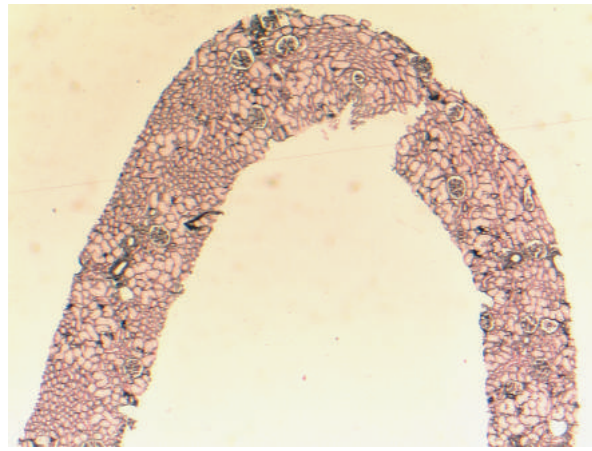
The most important pathogens are the Korean prototype *Hantaan* (HTNV) and *Seoul virus* (SEOV) in the Far-East, *Puumala virus* (PUUV) and *Dobrava-Belgrade virus* (DOBV) in the West, and *Sin Nombre* (SNV) and *Andes virus* (ANDV) in the Americas. A novel, and sometimes lethal, hantavirus seems to be present in India (Clement et al., 2006; Mani et al., 2012), causing both community-acquired acute kidney injury (CAAKI) and acute lung injury (ALI), but has not been recognized yet in a recent 26-year (1983–2008) study of CAAKI in Eastern India (Prakash et al., 2013). DOBV is the newest among pathogens in Europe and Russia, first mentioned in 1991 (Groen et al., 1991), and later characterized as a distinct serotype often inducing severe disease (Avsic-Zupanc et al., 1992). Recently, it became clear that four different subspecies of DOBV exist, tentatively now called Dobrava, Sochi, Kurkino, and Saaremaa, endemic in different regions of Central Europe or Russia, and causing in the same order decreasing grades of clinical severity, Saaremaa being probably very mild or subclinical (Maes et al., 2009; Klempa et al., 2013). 'Old World' hantaviruses target mainly the human kidney, resulting in the so-called haemorrhagic fever with renal syndrome (HFRS) (World Health Organization, 1983). A milder form of HFRS, aptly named 'nephropathia epidemica' (NE), caused by PUUV, is prevalent in European-Russia and Europe, and was clinically described in Sweden in 1934 (Myhrman, 1934), and in Finland even before the responsible viral agent was known (Lähdevirta, 1971; Lähdevirta et al., 1978). 'New World' hantaviruses target mainly the human lung, resulting in the so-called hantavirus pulmonary syndrome (HPS), first described in 1994 (Duchin et al., 1994). Nevertheless, the first seroconfirmed hantavirus cases in the New World (Brazil) were HFRS, not HPS cases (Hinrichsen et al., 1993). However, both HFRS and HPS are misnomers, because these 'syndromes' are rarely complete, and because there is a considerable overlap between the two (Clement et al., 1994c, 1997; Peters and Khan, 2002; Schütt et al., 2004; Rasmuson et al., 2011; Gizzi et al., 2013). So, the 'transatlantic dichotomy' between HFRS and HPS is now more and more questioned (Clement et al., 2012). Finally, the rat-transmitted SEOV, a serotype heavily endemic in the Far East, but recently also described in the West (Jameson et al., 2013; Macé et al., 2013; Taori et al., 2013), is a pathogen involving not only the kidney, but the liver as well, thereby resembling some forms of viral hepatitis, or some pregnancy-related emergencies.

Transmission of the disease

Preferred biotope and natural cycle of the rodent carriers determine the geographical spread and intensity of local hantavirus disease (Table 188.1). For instance, bank voles (*Myodes glareolus*), the reservoirs of PUUV, thrive in a 'wet habitat', so that the humid and temperate forests of West and Central Europe, or the boreal forests (taiga) in North Europe, both with a protective thick understory, are their preferred biotope (Clement et al., 1994b). This often overlooked fact explains why NE is virtually absent from most of Southern Europe, whose predominant biotope, the bare 'Mediterranean shrub', is much drier (Clement et al., 2010). The conspicuous absence, however, of NE cases registered in the United Kingdom, despite sufficient presence of beeches and oaks







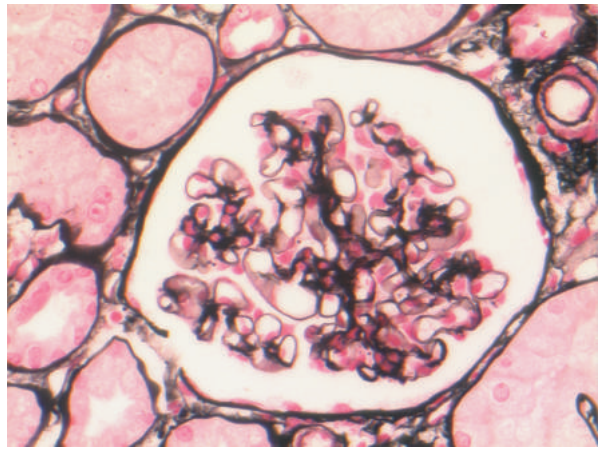


Fig. 188.1 Species of hantaviruses.

(see 'Epidemiology'), bank voles, and humidity, remains hard to explain, even taking a lower local medical awareness into account (Bennett et al., 2006). On the European continent, during the first reported NE outbreaks in Belgium (1986), the Netherlands (1989), Germany (1990), and across the Franco-Belgian border (1993), local capture actions of bank voles yielded a presence of PUUV antigen in their lungs, which was each time significantly higher than the degrees of bank vole PUUV infection that were demonstrated (if ever) before in the same countries (Clement et al., 1994a, 1998). In the United Kingdom, however, no sero-epidemiological studies have so far assessed specifically PUUV or other hantavirus species in humans or rodents. Only very recently, 495 wild rodents (including 133 brown rats and 35 bank voles) were captured and found negative, except for a field vole yielding a novel hantavirus (*Tatenale virus*) without known pathogenicity to date (Pounder et al., 2013). Remarkably, the first and only clinical series so far of seroconfirmed HFRS on the British Isles dates back to 1994 and originated from Northern Ireland, the only region in West Europe where bank voles and other known rodent reservoirs of pathogenic hantaviruses are totally absent, except for the cosmopolite wild rat, carrier of SEOV. A total of 15 SEOV-induced acute kidney injury (AKI) cases (mostly farmers with rat exposure) were found, constituting up to now the only European registry of SEOV nephropathy caused by wild rats (McKenna et al., 1994). Interestingly, other recent cases of SEOV nephropathy in England and Wales were recently confirmed, and a SEOV strain, called *Humber virus*, was isolated from a wild rat captured at a patient's residence, hereby constituting the first isolation of a pathogenic hantavirus from a wild rodent in the United Kingdom (Jameson et al., 2013; Taori et al., 2013).

During recent years, at least 29 'new' hantaviruses have been characterized in different insectivores (shrews and moles) and/or bats instead of rodents, both from the Old and New World (Guo et al., 2013). However, no human pathogenicity has been described so far, except for a preliminary and retrospective clinical description of two cases in the 1980s in Belgium, apparently infected by a mole and by a water shrew (Clement et al., 2011).

Remarkably, some totally novel viruses have very recently been discovered, showing in their clinical presentation some resemblances to HTVD. In China and Japan, 'severe fever and thrombocytopenia syndrome virus' (SFTSV), another bunyavirus, but tick-borne and belonging to the *Phlebovirus* genus, can cause an often fatal (12–30%) multiorgan failure, with proteinuria (84%) and haematuria (59%) (Yu et al., 2011). Just like in HFRS, the human host reacts with a 'cytokine storm', which seems to be pivotal in the pathogenesis (Sun et al., 2012). Recently, *Heartland virus*, another novel tick-borne phlebovirus, genetically related to SFTSV, was discovered in the United States, which causes fever, diarrhoea, thrombocytopenia, and leucopenia (McMullan et al., 2012). A novel coronavirus (nCoV), originating from bats, and related to the aetiologic agent of SARS (severe acute respiratory syndrome) was found in the Middle East, causing lethal cases of ALI, often complicated by AKI (Zaki et al., 2012).

General pathogenetic mechanisms of hantaviral diseases

Hantaviruses target endothelial cells, macrophages, dendritic cells, and platelets through interactions between viral Gn/Gc glycoproteins and cell surface β3 integrin receptors (Jonsson et al., 2010). Immune activation leads to excessive production of pro-inflammatory cytokines, such as tumour necrosis factor (TNF), interleukin (IL)-2, IL-6, and interferon (IFN). These proinflammatory cytokines cause endothelial injury leasing to increased permeability in microvascular beds of the kidney, haemorrhage into tissues, and shock (Jonsson et al., 2010; Terajima and Ennis, 2011).

The major histocompatibility complex (MHC) molecule can influence the hantaviral disease outcome. MHC class I and II molecules present different sets of viral peptides to CD8+ and CD4+ T cells which may be responsible for the immunopathogenesis. For example, the human leucocyte antigen (HLA)-B8-DR3 extended haplotype is associated with severe outcome of NE caused by PUUV infection, in contrast to HLA-B27 with a milder disease in Finland. The HLA-DRB1*09 allele was associated with HFRS in Chinese (Terajima and Ennis, 2011).

Endothelial cells are first and most frequently infected by (pathogenic) hantaviruses, where, without noticeable morphological changes, they cause a transient deficit of the endothelial barrier function, resulting in increased permeability, or a so-called capillary leakage syndrome, which can be lethal, particularly in the heart and lungs. The rapidity of appearance and spontaneous disappearance within weeks of proteinuria and AKI suggest a functional, rather than an anatomical lesion, as confirmed by the absence of glomerular lesions on kidney biopsy. As in many other emerging infections, the host immunological reaction seems more important than the infecting pathogen itself, resulting in a pro-inflammatory 'cytokine storm', with the lungs and kidney as main target organs (Maes et al., 2004). Release of cytokines or vascular endothelial growth factor was proposed as mechanism in the pathogenesis (Shrivastava-Ranjan et al., 2010). Very recently, increased levels of bradykinin were detected in the supernatants of hantavirus-infected endothelial cells, inducing markedly increased permeability. Bradykinin is a potent inducer of inflammation and most notably, of vascular leakage (Taylor et al., 2013). Moreover, the TNF-α polymorphism (Maes et al., 2006) and HLA-B8-DR3 haplotype in the human host seem to be determinants for the severity of hantavirus disease, at least in PUUV infections (Mäkelä et al., 2002).

American authors found that pulmonary effusions in HPS can have almost the same protein composition as plasma (Peters and Khan, 2002), suggesting a endothelial barrier breakdown similar to the temporary deficit of the glomerular endothelial barrier function in HFRS. Terajima and Ennis (2011) suggested that capillary leakage observed in HPS and HFRS may be caused by a common immunopathological mechanism, that is, hantavirus-specific cytotoxic $CD8^+$ T lymphocytes, attacking endothelial cells that present viral antigens on their surface. Krautkrämer et al. (2011) showed that monolayers of human glomerular endothelial cells are preferentially infected *in vitro* by Old World hantaviruses (Asian HTNV and European PUUV), disturbing the structure and integrity of cell-to-cell contacts, as demonstrated by redistribution and reduction of the tight junction marker, protein ZO-1. This ZO-1 anomaly of the tight junctions was more pronounced in renal biopsy specimens from hantavirus-infected patients than from non-infected individuals. Furthermore, the decrease in glomerular ZO-1 correlated significantly with the decrease of serum albumin, and was most marked in podocytes. Finally, ZO-1 presence and localization were not altered in kidney biopsies from non-hantaviral acute tubulointerstitial nephritis (ATIN) forms, in

Table 188.1 A summary of the major causative hantaviruses and their rodent reservoirs

Group and subfamily		Strain and abbreviation	Rodent reservoir	Major distribution area
Old World hantavirus (mainly cause haemorrhagic fever with renal syndrome, HFRS)	*Murinae*	Hantaan virus, HTNV (severe HFRS with mortality rates up to 15%)	*Apodemus agrarius*	China, Korea, Russia
		Dobrava-Belgrade virus, DOBV (severe HFRS with mortality rates up to 12%)	*Apodemus flavicollis*	Balkans
		Seoul virus, SEOV (moderate HFRS with a mortality rate of < 1%)	*Rattus norvegicus*, *Rattus rattus*	Worldwide
		Saaremaa virus, SAAV	*Apodemus agrarius*	Central Europe
		Amur virus, AMRV	*Apodemus peninsulae*	Far East Russia
	Arvicolinae	Puumala virus, PUUV (causing nephropathia epidemica with a mortality rate of 0.1%)	*Clethrionomys glareolus*	Europe, Asia, and Americas
New World hantavirus (mainly cause hantavirus pulmonary syndrome, HPS)	*Sigmodontinae*	Sin Nombre virus, SNV (Deer mouse, *Peromyscus maniculatus*); Monongahela virus, MGLA (*Peromyscus leucopus*); New York virus, NYV (*Peromyscus leucopus*); Bayou virus, BAYV (*Oryzomys palustris* rodents); Black Creek Canal virus, BCCV (*Sigmodon hispidus* rodents)		North America
		Andes virus, ANDV (*Oligoryzomys longicaudatus*); Bermejo virus, BMJV (*Oligoryzomys chocoensis*); Choclo virus (*Oligoryzomys fulvescens*); Lechiguanas virus, LECV (*Oligoryzomys flavescens*); Maciel virus, MCLV (*Bolomys obscurus*); Oran virus, ORNV (*Oligoryzomys longicaudatus*); Laguna Negra virus, LANV (*Calomys laucha* rodents); Araraquara virus (*Bolomys lasiurus*); Juquitiba virus (*Oligoryzomys nigripes*)		South America

clear contrast to HFRS ATIN forms. This finding confirms again that HFRS should be differentiated from probably all other forms of ATIN, not only in epidemiology and clinical presentation (see earlier in chapter), but in pathophysiology as well.

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CHAPTER 189

Dengue and other viral haemorrhagic fevers

Jung-San Chang and Hung-Chun Chen

Dengue

Introduction

Dengue is a mosquito-borne viral disease caused by dengue virus (DENV), a positive-sense single-stranded RNA virus of the Flaviviridae family with four distinct serotypes (DENV-1, -2, -3, -4). The 11 kb DENV genome codes for three structural proteins, seven non-structural proteins, and has short non-coding regions on both the 5′ and 3′ ends. Structural proteins include capsid protein C, membrane protein M (prM/M protein for formation and maturation of the viral particle), and envelope protein E (for viral attachment to cellular ICAM3-grabbing non-integrin, CD209, Rab 5, GRP 78, and the mannose receptor, for viral entry). Non-structural proteins include NS1, NS2a, NS2b (cofactor of NS3 to form the active site), NS3 (serine protease, RNA helicase, RTPase/NTPase), NS4a, NS4b, and NS5 (N-terminal is methyltransferase; C-terminal end is RNA-dependent RNA polymerase) (Schmaljohn and Nichol, 2007; Peters, 2008).

Dengue fever (DF) is endemic in > 100 countries, especially in the tropics and subtropics (Guzman and Kouri, 2002; Peters, 2008). Human infection is through a mosquito–human–mosquito cycle in urban areas. The most common vector is *Aedes aegypti. Aedes albopictus, Aedes scutellaris*, and *Aedes polynesiensis* mosquitoes may be the vectors in certain areas. Dengue infection causes a range of clinical presentations. The World Health Organization (WHO) classified DENV infection into asymptomatic infection, DF, dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS) (WHO, 1997). However, the WHO classification has been criticized (Deen et al., 2006).

Clinical features

The disease spectrum has been re-categorized into dengue with or without warning signs and severe dengue (WHO, 2009). It is estimated that the ratio of asymptomatic to apparent infection is about 15:1 for primary infection (Peters, 2008). The classic DF is a fever–arthralgia–rash syndrome. After an incubation period of 3–14 days, it begins with the abrupt onset of fever and constitutional symptoms such as severe headache, myalgia, arthralgia, back pain, eyeball/retro-orbital pain, anorexia, nausea, and skin rash. The skin rash spares palms and soles, and evolves from initial phase of widespread erythema to maculopapular and purpuric stages (Guzman and Kouri, 2002; Peters, 2008). Myalgia and deep bone pain (breakbone fever) are characteristic. Also notable are absence of cough and coryza. Leucopenia, thrombocytopenia, and elevated transaminases are common, but the erythrocyte sedimentation rate is normal in most cases. Lifelong protection against that serotype persists after recovery, but cross-protection between serotypes is only transient. DHF is a severe form of DENV infection with fever, haemorrhage manifested by positive tourniquet test, petechiae, or bleeding, thrombocytopenia, and signs of plasma leakage. The risk of developing DHF is 0.2% during the first infection, but increases at least 10-fold after a second DENV infection. Severe DHF is characterized by compromised circulation and shock (DSS).

DHF can be complicated with hepatitis, azotaemia, cardiac impairment, and/or encephalopathy. Renal manifestations include haematuria, proteinuria, glomerulonephritis, acute kidney injury (AKI), and haemolytic uraemic syndrome (Lima and Nogueira, 2008; Lee et al., 2009). The incidence of AKI in DHF/DSS patients ranges from 0.3% to 5% with a mortality of around 30–40% (Lima and Nogueira, 2008). AKI can be due to acute tubular necrosis secondary to hypotension, rhabdomyolysis, haemolysis, or the use of nephrotoxic agents, or secondary to acute glomerulonephritis, as a result of immune-mediated renal injury secondary to DENV infection.

Pathogenesis

DHF usually occurs as secondary infection in individuals with pre-existing non-neutralizing antibodies against other serotypes. Immune complexes formed by the virus and non-neutralizing antibodies promote infection of mononuclear cells through interaction between Fc portion of immunoglobulin (Ig)-G and Fcγ receptors of mononuclear cells, the so-called antibody dependent enhancement (Guzman and Kouri, 2002). DENV may infect immune cells to modulate innate immunity. In addition, T-cell-mediated immunity, intrinsic viral properties, and host genetic determinants have been implicated in affecting disease severity (Pagni and Fernandez-Sesma, 2012). The severity of DHF is related to the suboptimal activation of innate immunity and release of interleukin (IL)-2, IL-6, IL-8, tumour necrosis factor alpha, and interferon gamma. These immune complexes also activate the classic complement pathway, which promote plasma leakage and DSS (Guzman and Kouri, 2002). In mice, binding of DENV to CLEC5A molecules on the mononuclear cells triggers DAP12 signalling, leading to the release of large amount of proinflammatory cytokines (Chen

Table 189.1 World Health Organization classification of dengue haemorrhagic fever

Grade I	Fever associated with non-specific constitutional symptoms and with a positive tourniquet test and/or easy bruising
Grade II	Spontaneous bleeding with the manifestations of grade I
Grade III	Circulatory compromise manifested by rapid, weak pulse and narrowing of pulse pressure (20 mmHg or less), or hypotension, with restlessness and cold clammy skin
Grade IV	Profound shock with undetectable blood pressure or pulse

The tourniquet test is performed by inflating a blood pressure cuff to the midpoint between systolic and diastolic pressures for 5 minutes and then releasing the pressure. The appearance of > 20 petechiae per square inch below the cuff confirms the positive test (WHO, 1997).

et al., 2008), followed by increased endocapillary and mesangial cellularity, glomerular IgM deposition 48 hours after infection, and diffuse proliferative glomerular injury 14 days after infection (Lima and Nogueira, 2008).

Pathology

Grossly, the kidneys may be swollen and exhibit petechial haemorrhages. Light microscopy shows hypertrophy and hyperplasia of mesangial and endothelial cells, irregular thickening of the capillary wall, perivascular infiltration of mononuclear cells, and focal thickening of the glomerular basement membrane. Immunofluorescence reveals IgG, IgM, and low intensity of C3 in the mesangium. Electron microscopy shows focal effacement of the foot process of podocytes. Intact and degenerated mononuclear phagocytes trapped between the endothelial cytofolds can be found in glomerular capillary lumina. In fatal DHF/DSS patients, DENV can be found in renal tubular cells (Boonpucknavig and Soontornniyomkij, 2003; Jessie et al., 2004).

Diagnosis

The diagnosis should be suspected in anyone who develops an acute febrile illness with two or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, haemorrhagic manifestations, or leucopenia) at the same place and time as other confirmed cases of dengue fever. Confirmation of DENV infection requires demonstration of positive reverse-transcriptase polymerase chain reaction (RT-PCR) for dengue virus RNA in serum, DENV isolation, dengue-specific IgM antibody titre ≥ 1:40 in acute phase serum, or at least a fourfold increase of dengue-specific IgG titres in paired convalescent-acute phase sera (Lee et al., 2009). Differential diagnosis includes other infectious diseases with overlapping presentations such as leptospirosis (see Chapter 191) and hantavirus infection (see Chapter 188). Hantavirus infection is rare in tropical regions (Lima and Nogueira, 2008).

Patients are labelled as having DHF when they exhibit a haemorrhagic tendency shown by a positive tourniquet test or spontaneous bleeding, thrombocytopenia (platelet count < $10 \times 10^4/\mu L$), and evidence of plasma leakage, as shown by a > 20% increase in haematocrit compared with the corresponding value at discharge, a haematocrit decrease > 20% after rehydration, presence of pleural effusion, ascites, and/or hypoproteinaemia (< 3.5 g/dL) (WHO, 1997). DHF is further classified into four grades of illness by the WHO (Table 189.1). Grades III and IV are grouped as DSS, in which shock is present in association with all four DHF defining criteria (WHO, 1997).

Management

Treatment is mainly supportive, including maintenance of blood pressure, monitoring of vital signs, blood loss, and electrolyte imbalance, judicious fluid therapy to avoid dangerous overhydration, treatment of the secondary bacterial infections, avoidance of non-steroidal anti-inflammatory drugs and other nephrotoxic agents, and management of complications. Fluid can be re-absorbed from third spaces that cause high-output heart failure and pulmonary oedema, especially if the patient is over-hydrated. Intramuscular and subcutaneous injections are contraindicated because of the risk of bleeding. Multivalent vaccines have been developed but are not yet available commercially. The mortality rate of DHF can be as high as 15%, but can be reduced to < 1% with careful management (Kuo et al., 2008; Peters, 2008).

Other viral haemorrhagic fevers

Other viruses that can have renal involvement belong to four viral families: Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae. Examples include yellow fever (Flaviviridae), Omsk haemorrhagic fever (Flaviviridae), South American haemorrhagic fever (Arenaviridae), Lassa fever (Arenaviridae), Rift Valley fever (Bunyaviridae), Crimean-Congo haemorrhagic fever (Bunyaviridae), Ebola haemorrhagic fevers (Filoviridae), Marburg haemorrhagic fevers (Filoviridae) (Bausch and Ksiazek, 2002; Lima and Nogueira, 2008), and severe fever with thrombocytopenia syndrome virus (SFTSV; Bunyaviridae) (Yu et al., 2011). Most of these associations have been described as case reports and causality has not been established as well as with the other infections.

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CHAPTER 190

Yellow fever, severe acute respiratory syndrome virus, and H1N1 influenza infections

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Yellow fever

Epidemiology

Yellow fever is a mosquito-borne, viral haemorrhagic fever endemic in tropical areas of Africa and South America, caused by the yellow fever virus, considered as the prototype for the *Flavivirus* genus and Flaviviridae family. The name yellow fever originated from the striking jaundice observed in the severe cases of this disease. The World Health Organization (WHO) estimates that a total of 200,000 cases of yellow fever occur each year, with about 30,000 deaths. More than 90% of the cases occur in Africa, where > 500 million people live in the yellow fever at-risk zone between 15° north and 15° south of the equator. Furthermore, yellow fever is a significant risk to > 3 million travellers who visit areas affected with yellow fever each year. Exposure of susceptible persons to bites from infected mosquitoes is the only significant mode of yellow fever transmission. An urban and a jungle (forest, sylvatic) form of yellow fever can be distinguished by differences in their respective transmission cycles. Urban yellow fever, which frequently occurs as large outbreaks, is transmitted from infected to susceptible humans by *Aedes aegypti*, a mosquito species that breeds in the proximity of human habitats. The urban form of transmission is found mainly in Africa. The jungle form of yellow fever is primarily an enzootic viral disease of non-human primates, but the mosquito vectors may occasionally cause individual cases or small outbreaks of yellow fever among humans in the forested savannah of Africa and in jungle areas of South America.

Since the beginning of the 1980s, the incidence of yellow fever has increased dramatically, particularly in Africa, despite the availability of an effective vaccine. Disease severity is highest in the elderly and infants with significant post-infection morbidity (for review, see Murthy et al., 2013). In North and South America, the urban cycle was extinguished in the 1940s and 1950s, although resurgence was documented recently in Bolivia (for review, see Lima and Nogueira, 2008).

Clinical symptoms

Yellow fever is a multisystem viral sepsis, which might be asymptomatic or may evolve into a clinical spectrum ranging from a non-specific febrile disease to a severe and fatal haemorrhagic illness associated with shock, liver, kidney, heart, and nervous system injury. Following a bite of an infected mosquito, the incubation period is approximately 3–6 days. This is followed by either subclinical infection, non-specific illness, transient influenza-like disease, a febrile illness with jaundice, or fatal haemorrhagic fever. Disease onset is typically abrupt and characterized by fever, chills, malaise, headache, lower back pain, generalized nausea, and dizziness. Congestion of the conjunctiva and face, as well as relative bradycardia, is commonly found. In patients with a transient, non-icteric infection, the average duration of fever is 3–4 days, followed by complete recovery. However, in approximately 15% of cases, the disease progresses, with or without a brief (24–48 hours) remission, to a more severe form, with fever, vomiting, epigastric pain, jaundice, renal failure, and haemorrhagic manifestations, characterized by petechiae, ecchymoses, epistaxis, and haematemesis (the characteristic yellow fever 'black vomit'). About 20–50% of patients with hepatorenal failure die, in most cases 7–10 days after onset of disease.

Renal involvement

The kidneys are frequently cited as target organs in severe cases of yellow fever, but consistent information about the types, prevalence, and mechanisms of the associated kidney injury is scarce. Oliguria has been described to occur after 5–7 days in severe yellow fever (Gardner and Ryman, 2010). Gross pathology of fatal human yellow fever usually revealed grossly enlarged, congested, and oedematous kidneys. Renal histology disclosed acute tubular necrosis (Gardner and Ryman, 2010). Studies performed in rhesus monkeys suggest that prerenal mechanisms predominate until the late phase of the disease, when frank acute tubular necrosis develops (Monath et al., 1981; Monath, 2001; Monath and Barrett, 2003). In severe disease, the presence of microcirculatory failure and tissue ischaemia, due to shock and disseminated intravascular coagulation associated with extremely high bilirubin levels, are possible mechanisms for acute kidney injury (AKI). The finding of viral antigens in the renal epithelium of three fatal cases of yellow fever and the virus isolation from renal tissue from patients with yellow fever vaccine-induced viscerotropic disease (De Brito et al., 1992; Vasconcelos et al., 2001), suggest a possible direct effect of the virus on the kidneys. Yellow fever viral antigens were detected in glomeruli 2–3 days after experimental inoculation in monkeys (Monath and Barrett, 2003), and renal structural changes culminating

in renal cell necrosis were observed 24 hours after infection in a murine yellow fever model (Gershy-Damet, 1984).

Treatment and prevention

No specific treatment exists for yellow fever and supportive care is critical. The management consists of vasoactive medications, fluid resuscitation, ventilator management, and treatment of disseminated intravascular coagulation, haemorrhage, secondary infections, and renal and hepatic dysfunction.

A single yellow fever vaccination provides sufficient immunity against the disease, negating the need for booster vaccinations every 10 years, according to a study by the WHO's Strategic Advisory Group of Experts. The report, based on a review of the available data, including two systemic reviews, also found that vaccination failures are extremely rare and that such failures do not cluster as the time following vaccination increases (WHO, 2013).

Severe acute respiratory syndrome virus

Severe acute respiratory syndrome (SARS) is caused by the SARS coronavirus. The outbreak of SARS started in Asia in 2003 and then expanded elsewhere in the world. Symptoms include muscle pain, headache, lymphopenia, and fever, followed in 2–10 days by the onset of respiratory tract symptoms, namely cough, dyspnoea, and pneumonia. The overall mortality rate was 9%. In patients > 50 years old, the mortality rate approaches 50%. AKI has been observed in patients with rhabdomyolysis. A study in Hong Kong in 2003 showed that 6.7% of cases developed acute renal impairment occurring at a median duration of 20 days (range 5–48 days) after the onset of disease. The mortality rate was higher among SARS patients with renal impairment (91.7% vs 8.8%). Autopsy findings revealed acute tubular necrosis (Chu et al., 2005).

In Taiwan, Huang et al. (2005) identified 13 AKI patients from a total of 78 probable SARS cases admitted to a single hospital. AKI developed 7.2 ± 4.3 days after admission. Comorbidities of diabetes and heart failure were more common in patients who developed AKI and the incidence of respiratory failure and mortality (77% vs 8%, $P < 0.001$) were also higher. Multiple organ system failure usually accompanied AKI. Hypotension (77%) and rhabdomyolysis (43%) were associated with AKI.

H1N1 influenza viral infections

In late March and early April 2009, an outbreak of H1N1 influenza A virus infection was detected in Mexico, rapidly spreading to other countries as a result of airline travel. On 11 June 2009, the WHO raised its pandemic alert to the highest level. This pandemic was caused by an H1N1 influenza A virus strain that represents a quadruple reassortment of two swine, one human, and one avian strain of influenza. This novel virus infection has caused about 17,000 deaths by 2010, although it is likely that the true numbers of cases are many times higher than the confirmed ones.

Some typical clinical features of H1N1 infection are its easy airborne spreading, with an apparent predilection of affecting young individuals, with an estimated age range between 5 and 59 years in Mexico, and affecting very young and very old people in the United States, similar to the age distribution that is described with seasonal influenza (Centers for Disease Control and Prevention, 2009). Symptoms of zoonotic swine flu in humans are similar to those of influenza, namely chills, fever, sore throat, muscle pains, severe headache, and coughing.

Common risk factors for H1N1 complications include chronic lung disease, immunosuppressive states, cardiac disease, pregnancy, diabetes, and obesity (Trifonov et al., 2009). Both leucopenia and leucocytosis, elevated liver aminotransferases, elevated lactic dehydrogenase, and creatine phosphokinase have been described. The latter findings could be explained by associated rhabdomyolysis. Recently a 28-year-old female and a 19-year-old male with AKI in the course of H1N1 influenza infection due to rhabdomyolysis were described (Unverdi et al. 2011).

Trimarchi et al. (2010) described 22 patients with H1N1 pneumonia, 14 (63.6%) of whom developed AKI with mean peak creatinine levels of 2.74 ± 2.83 mg/dL. Four (18.2%) needed renal replacement therapy (RRT) with a mean duration of 15 ± 12 days. Six patients (42.9%) recovered renal function. AKI was associated with pregnancy, immunosuppression, high APACHE, SOFA, and MURRAY scores, and less time on mechanical ventilation, haemodynamic instability, and thrombocytopenia. Haemodialysis (HD) requirements were associated with elevated SOFA scores (12.25 ± 1.75 vs 6.22 ± 0.8, $P < 0.05$), elevated creatine phosphokinase (933 ± 436.6 vs 189.9 ± 79.3 U/L, $P < 0.05$), and alanine transferase levels (843.3 ± 778.8 vs 85.33 ± 17.4 U/L, $P < 0.05$). Twelve patients died (54.6%), 10 of whom had AKI (83.3%).

Vallejos et al. (2013) described the outcome in 44 patients with PCR-confirmed H1N1 and who all needed RRT. The average time between admission to the intensive care unit and initiation of RRT was 3.16 ± 2.6 days. At initiation of RRT, most patients required mechanical ventilation. No relationship was found with creatinine kinase levels. Seventy-five per cent of the cases were observed during a 3-week period and mortality, related to respiratory failure, doubling of alanine amino transferase, and use of inotropes was 81.8%. The reported characteristics of AKI associated with H1N1 are not different from those reported for seasonal influenza and the renal involvement is part of a systemic inflammatory response syndrome, viral sepsis, with multiorgan failure.

Finally, Bagshaw et al. (2013) performed a prospective multicentre Canadian cohort study of critically ill patients with confirmed or probable pH1N1 infection and described the incidence and severity of AKI and the rates of RRT utilization along with risk factors for AKI, RRT, and mortality. AKI occurred in 60.9%, with RIFLE categories of Injury (23.0%) and Failure (37.9%). Independent predictors of AKI included obesity, chronic kidney disease, APACHE II score, and PaO_2/FiO_2 ratio. Of patients with AKI, 24.9% (85/342) received RRT and 25.8% (85/329) died. Thus both of these recent studies underline that H1N1-infected patients who develop RRT-requiring AKI, in the context of multiorgan failure, show a high mortality rate.

Besides intensive therapeutic support, it was recently found that timely oseltamivir administration has a beneficial effect on outcomes in hospitalized adults with H1N1, even in those who are admitted beyond 48 hours after onset of symptoms (Viasus et al., 2011).

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CHAPTER 191

Leptospirosis

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Introduction

Leptospirosis is an infectious disease caused by the spirochaete of the genus *Leptospira*. There are at least 12 pathogenic and four saprophytic species, with almost 300 pathogenic *Leptospira* serovars. Immunity after infection is limited to antigenically related serovars. Several mammals such as rats, dogs, pigs, cattle, and horses are natural carriers and vectors of pathogenic leptospires, which colonize the renal tubules of the infected hosts. The spirochaetes are shed in urine to the environment, where they can survive for months in suitable conditions. Humans are usually infected through broken skin or mucosal membranes upon contact with contaminated urine, water, or soil. Individuals working with animals or potentially contaminated material, such as farmers, pet traders, veterinarians, rodent exterminators, slaughters, garbage collectors, and sewer workers, have an increased risk of acquiring leptospirosis. Outbreaks are noted in periods of high rainfall, or after natural disasters, such as floods or hurricanes.

Leptospirosis is a broadly spread zoonotic disease worldwide, occurring both in developed and developing countries. Although more frequent in tropical and subtropical areas, it is present in all continents except Antarctica. The increase in urbanization and the expanding of international tourism and outdoor activities in countries where leptospirosis is endemic resulted in an increase in the worldwide incidence of this disease (Adler and la Peña Moctezuma, 2010; Hartskeerl et al., 2011). Leptospirosis has a particularly high prevalence in South East Asia and Latin America. Recent serious outbreaks occurred in Nicaragua, Sri Lanka, and the Philippines, causing significant morbidity and mortality (Hartskeerl et al., 2011). Leptospirosis is considered a major public health problem due to its striking global re-emergence. The current estimate of half a million of cases annually likely underestimates the real burden of the disease, since leptospirosis is difficult to diagnose and is frequently neglected (Jha and Chugh 2008; Lombardi et al., 2008; Adler and la Peña Moctezuma, 2010; Hartskeerl et al., 2011; Forbes et al., 2012).

Clinical features

The clinical picture of leptospirosis is extremely variable, ranging from an asymptomatic infection or a mild flu-like disease to severe, life-threatening forms (Adler and la Peña Moctezuma, 2010; Hartskeerl et al., 2011; Forbes et al., 2012). The causal serovar and the immune competence of the affected individual are considered important factors for the modulation of the severity of the disease (Hartskeerl et al., 2011).

Leptospirosis has in the earlier phase an elusive onset with unspecific symptoms of fever, myalgia, and headache. Clinical features evolve over 4 days after the initial symptoms, to chills, diarrhoea, nausea and vomiting, decrease in urinary output, rubinic jaundice, conjunctival suffusion, aseptic meningitis, haemorrhages, joint pain, skin rash, cough, cardiac arrhythmias, and central nervous system disturbances such as psychosis and/or delirium. The most severe form of leptospirosis, called Weil disease, occurs in approximately 10% of the patients, and is characterized by acute kidney injury (AKI), liver failure, and pulmonary haemorrhage (Hartskeerl et al., 2011; Forbes et al., 2012; Seguro and Andrade, 2013). Weil disease may progress to cardiovascular collapse and acute respiratory distress syndrome, with a high mortality rate (Andrade et al., 2008).

Kidney involvement is nearly universal in leptospirosis. The organisms infiltrate renal tissue causing acute interstitial nephritis. The urinary sediment may show leucocyturia, haematuria, bile pigments, and granular casts. Proteinuria, if present, is typically < 1 g/24 hours (Daher et al., 2010; Seguro and Andrade, 2013). Clinically, leptospirosis-induced renal dysfunction may be manifested as a tubulopathy characterized by electrolyte wasting and/or by the development of AKI (Seguro et al., 1990; Andrade et al., 2008; Sitprija, 2008; Khositseth et al., 2008; Daher et al., 2010).

Tubular abnormalities, comprising glucosuria, bicarbonaturia, uricosuria, and high urinary excretion of sodium, potassium, phosphate, and magnesium, precede and might occur independently of the fall in glomerular filtration rate. Leptospirosis-induced hypokalaemia and hypomagnesaemia are frequent and cases of hypokalaemic paralysis and symptomatic hypomagnesaemia have been reported (Seguro et al., 1990; Abdulkader et al., 1996; Krishnan et al., 2003; Andrade et al., 2008; Khositseth et al., 2008; Spichler et al., 2008a; Craig et al., 2009; Baburaj et al., 2012; Singh, 2012). Urinary concentration ability defects can continue for long time after the disease resolution (Daher et al., 2004).

Leptospirosis-induced AKI occurs in 14% to 60% of the affected patients (Sethi et al., 2010; Agampodi et al., 2011; Schelotto et al., 2012). Although it is more common in patients with Weil disease, AKI can also occur in non-icteric patients (Hurst et al., 2009). Leptospirosis-induced AKI is usually non-oliguric (Seguro et al., 1990; Daher et al., 2009) and hypokalaemia is common in these patients (Seguro and Andrade, 2013). Non-oliguric patients need dialysis less frequently and recover renal function sooner than oliguric patients (Seguro et al., 1990).

Pathology

Tubulointerstitial nephritis is the principal and universal renal structural injury found in leptospirosis. The infiltrate is mostly composed of mononuclear cells. Intact leptospires can be found by

immunohistochemistry throughout the tubular basement membrane, among tubular cells, within the tubular lumens, within the interstitium, and, more rarely within the glomeruli. Fragments of spirochaetes have been found within histiocytes, in the interstitium, and in tubules. The glomeruli have a normal aspect or show mild mesangial proliferation (Penna et al., 1963; Daher et al., 2010; Seguro and Andrade, 2013). Experimental studies demonstrated leptospires in the mesangium and in the renal interstitial compartment 3–6 hours after inoculation of *Leptospira icterohaemorrhagiae* (Daher et al., 2010).

Aetiopathogenesis of the renal dysfunction

Diverse mechanisms have been related to leptospirosis-induced tubular dysfunction, such as leptospira glycolipoprotein (GLP)-induced resistance to the action of vasopressin on the distal tubules (Cesar et al., 2012), effect of GLPs on tubular Na-K-ATPase activity (Younes-Ibrahim et al., 1995), decreases in endogenous sodium/hydrogen exchanger isoform, aquaporin 1, and alpha-Na^+K^+ATPase expression in proximal convoluted tubule cells (Araujo et al., 2010), and activation of toll-like receptor (TLR)-dependent pathway (Yang et al., 2006). Development of hypokalaemia has been associated with increased serum levels of cortisol and aldosterone (Abdulkader et al., 1996).

Multiple mechanisms are involved in the genesis of leptospirosis-induced AKI (Droulias et al., 2007; Andrade et al., 2008; Daher et al., 2010; Dassanayake et al., 2012; Seguro and Andrade, 2013). The outer membrane of the renal infiltrating leptospira has several antigenic proteins capable of causing renal injury. Among them, LipL32 is the most important, increasing the expression of pro-inflammatory cytokines and activating the renal nitric oxide pathway (Yang et al., 2002). Hypovolaemia due to vomiting, diarrhoea, fever, haemorrhages, and sepsis-induced vasodilation and hypotension can cause severe systemic and renal haemodynamic disturbances leading to renal ischaemia. Elevated levels of bilirubin worsen the vasodilation and have direct toxic effect on tubular cells. Finally, leptospirosis-induced rhabdomyolysis can also contribute to the development of AKI due to the deleterious effects of myoglobin on vascular resistance and tubular cells.

Treatment

There is no consensus on antibiotic treatment in leptospirosis. A Cochrane meta-analysis concluded that the available data are insufficient to advocate the use of antibiotics, but suggested the use of penicillin and doxycycline, since they seem to provide more benefit than harm (Brett-Major and Coldren, 2012). Antibiotic treatment was associated with shortened disease time, reduced length of hospital stay, and lower frequency of AKI, but did not change the mortality rate (Daher et al., 2012). Antibiotic administration rescued tubular function in an experimental model of severe leptospirosis (Spichler et al., 2007). Severe leptospirosis should be treated with intravenous penicillin (1,500,000 U every 6 hours), or ceftriaxone (1 g once daily), or cefotaxime (1 g every 6 hours). Oral azithromycin, amoxicillin, ampicillin, erythromycin, or doxycycline can be used in milder forms of the disease. Treatment should be kept for 7 days. As in other spirochaetal infections, Jarisch–Herxheimer reactions, characterized by fever, tachycardia, rigors, and hypotension, can develop with the initiation of antibiotic therapy (Daher et al., 2012; Forbes et al., 2012; Seguro and Andrade, 2013).

The treatment of established AKI must include early dialysis. Andrade et al. showed that in leptospirosis-induced AKI associated with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation, timely dialysis initiation combined with daily dialysis sessions was associated a mortality rate of 16.7% compared to a mortality of 66.7% in those who dialysed on alternate days (Andrade et al., 2007).

Patients with pulmonary complications of leptospirosis, such as pulmonary haemorrhages and ARDS, should use a conservative fluid intake protocol and approaches to minimize lung injury, such as low tidal volume and high positive end-expiratory pressure, when mechanical ventilation is required (Andrade et al., 2008; Seguro and Andrade, 2013).

Prognosis

The prognosis of the mild and moderate forms of leptospirosis is good. Mortality in Weil disease is > 10%, but can be > 50%, when accompanied by ARDS and AKI. Other factors such as altered mental status, white blood cell count, thrombocytopenia, and electrocardiographic abnormalities have also been associated with higher mortality (Daher et al., 2012; Seguro and Andrade, 2013). Morbidity and mortality were lower in patients with non-oliguric AKI (Seguro et al., 1990). AKI, oliguria, and serum creatinine >3.0 mg/dL were identified as independent factors associated with higher mortality in leptospirosis patients (Daher et al., 1999; Spichler et al., 2008b).

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CHAPTER 192

Syphilis

Emmanuel A. Burdmann

Syphilis infections

Syphilis is caused by the bacterium *Treponema pallidum*. The transmission route is usually sexual, but prenatal contamination (congenital syphilis) and transmission by infected blood can also occur. The incidence and prevalence of syphilis declined progressively until the 1990s, but has shown an increase in the last decade, probably due to changes in the health system organization, modifications in sexual behaviour, and the emergence of the HIV/AIDS pandemic. In fact, syphilis is again endemic in several parts of the world, with outbreaks reported in several countries (Herbert and Middleton, 2012; Tucker et al., 2011; Anonymous, 2012; Van de Laar and Spiteri, 2012). Currently, it is often accompanied by HIV co-infection, with a majority of men who have sex with men, but heterosexual men and women are also affected (Pathela et al., 2011).

Despite being relatively easy to treat, syphilis carries a high public health burden because of its recent resurgence, the fact that it is frequently overlooked, and because it might have severe multisystem effects.

The occurrence of syphilis-induced kidney disease, usually in patients with secondary syphilis, has been known since the 1920s (Thompson, 1920). The most frequent clinical presentation of syphilis nephropathy is proteinuria, ranging from transient and/or mild proteinuria to nephrotic syndrome. Other presentations include nephritic syndrome, acute kidney injury, chronic kidney disease, renal gumma, salt-losing nephropathy, and congenital nephrotic syndrome in infants born from infected mothers (Hunte et al., 1993; Walker et al., 1984; Estévez, 2006; Chen et al., 2005; Woods, 2009).

Several forms of glomerulopathy have been described in patients with syphilis, with the most common being membranous glomerulopathy. Other histological lesions such as minimal change disease, rapidly progressive glomerulonephritis with crescents, mesangial proliferative glomerulonephritis, endocapillary proliferative glomerulonephritis, immunoglobulin A nephropathy, amyloid nephropathy, and more rarely interstitial nephritis have also been reported (Bhorade et al., 1971; Walker et al., 1984; Krane, 1987; Hunte et al., 1993; Tang et al., 1999; Chen et al., 2005). The mechanisms of syphilis-induced renal disease are likely immunologic, triggered by the treponemal antigens (Walker et al., 1984; O'Regan et al., 1976; Tourville et al., 1976; Gamble and Reardan, 1975). The kidney disease usually reverts with appropriate antibiotic therapy (Basker et al., 2007; Boslooper et al., 2010; Mora Mora et al., 2011), and immunosuppressive therapy is not usually required.

The key message is that syphilis must be considered as a possible cause of kidney disease in patients infected with HIV with proteinuria or glomerulopathy. Renal biopsy is necessary to differentiate between HIV-associated nephropathy and syphilis-induced glomerulopathies, since both kidney diseases have analogous clinical presentations, but syphilis-induced glomerulopathies may recover with syphilis successful treatment (Bani-Hani et al., 2010; Satoskar et al., 2010; Havill et al., 2011; Chen et al., 2012).

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CHAPTER 193

Rickettsiosis

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Introduction

Rickettsiae are obligate intracellular bacteria transmitted by arthropod vectors, such as lice, fleas, mites, and ticks, to a vertebrate host. The main infections caused by rickettsiae in humans share a similar clinical pattern, manifesting as an acute febrile disease accompanied by headache, articular and muscle pain, and malaise. On the other hand, the rickettsioses have different outcomes, ranging from mild to life-threatening illness. Mortality rate is as high as 50% for epidemic typhus, scrub typhus, and Rocky Mountain spotted fever (RMSF). The diagnosis of rickettsial infections is difficult due to the non-specific clinical presentation and the difficulty in the isolation or culture of the organism (Kelly et al., 2002; Richards, 2012).

Epidemic typhus

Epidemic typhus is a worldwide distributed disease caused by *Rickettsia prowazekii*, with the human louse (*Pediculus humanus corporis*) as a vector. *Rickettsia prowazekii* grows in the louse's gut and is excreted in its faeces. The disease is then transmitted to an uninfected human who scratches the louse bite (which itches) and rubs the faeces into the wound. The incubation period is 1–2 weeks.

This disease has been affecting the human race for > 500 years, and outbreaks and epidemics occur associated with louse infestation due to poor hygiene conditions related to social disruption, food shortage, and wars. Epidemics occurred throughout Europe and occurred during the English Civil War, the Thirty Years' War and the Napoleonic Wars. During Napoleon's retreat from Moscow in 1812, more French soldiers died of typhus than were killed by the Russians. Typhus epidemics killed inmates in the Nazi Germany concentration camps. Even larger epidemics in the post-war chaos of Europe were only averted by the widespread use of the newly discovered DDT to kill the lice on millions of refugees and displaced persons. Following the development of a vaccine during World War II, epidemics have usually occurred in Eastern Europe, the Middle East, and parts of Africa, particularly in Ethiopia. Epidemic typhus can have a high mortality if not treated early, with higher lethality in the older and the malnourished (Bechah et al., 2008). Data on epidemic typhus-related renal injury is extremely scarce. In one report, 31% of the affected patients showed elevated blood urea nitrogen concentrations (Raoult et al., 2004).

Murine typhus

Murine (endemic or flea-borne) typhus is caused by *Rickettsia typhi* and has a rodent flea *(Xenopsylla cheopis*) as the vector. It is one of the most frequent rickettsioses with worldwide distribution, and infects humans incidentally. Murine typhus is usually a self-limiting, mild febrile illness lasting for up to 2 weeks, with a low mortality rate. Because this disease has an undifferentiated clinical picture, it may be easily confused with other febrile conditions and its incidence is probably deeply underestimated (Kelly et al., 2002).

Renal involvement presents as, including proteinuria, haematuria, and acute kidney injury (AKI) (Whelton et al., 1968; Shaked et al., 1994; Whiteford et al., 2001; Hernández Cabrera et al., 2004; Centers for Disease Control and Prevention, 2009; Takeshita et al., 2010; Chaliotis et al., 2012; Chang et al., 2012). There are large inconsistencies in the reported frequencies of renal involvement in murine typhus, likely due to different methods and definitions for assessing renal injury. Most of the information comes from case reports and retrospective series, and prospective studies are scarce.

The frequency of AKI was reported as 7.8% in a 5-year prospective study of 90 adult patients with murine typhus in Greece (Chaliotis et al., 2012), whereas it was about 19% in retrospective series (Hernández Cabrera et al., 2004; Chang et al., 2012). Minor elevations in serum creatinine and blood urea nitrogen have been reported in 13–21% and in 3–36% of affected individuals, respectively (Shaked et al., 1994; Whiteford et al., 2001; Hernández Cabrera et al., 2004; Centers for Disease Control and Prevention, 2009). Proteinuria occurred in 18.9–85% of the cases and microscopic haematuria in 85% of the patients (Shaked et al., 1994; Hernández Cabrera et al., 2004). Renal abnormalities recover rapidly after the infectious disease resolution (Hernández Cabrera et al., 2004; Centers for Disease Control and Prevention, 2009). Histology studies are very scarce. Multifocal perivascular interstitial nephritis was described in a renal biopsy from a surviving patient who developed AKI and in an autopsy case (Walker et al., 1989; Shaked et al., 1994).

The mechanisms of murine typhus-associated renal injury are not well known. Massive intravascular haemolysis associated with glucose-6-phosphate dehydrogenase deficiency, renal hypoperfusion secondary to intravascular volume depletion caused by increased vascular permeability, interstitial inflammation, direct action of the pathogen on renal tissue, and delayed or inadequate antibiotic treatment are considered as potential contributory factors for development of kidney injury (Whelton et al., 1968; Walker et al., 1989; Shaked et al., 1994; Chaliotis et al., 2012).

Scrub typhus

Scrub typhus, also known as chigger-borne rickettsiosis, tsutsugamushi disease, tropical or rural typhus, is caused by the bacteria

Orientia tsutsugamushi and has the *Leptotrombidium* mite larva (called chiggers) as vector. Because of significant differences in the RNA and cell wall structure this bacteria was removed from the genus *Rickettsia* and moved to the new genus *Orientia*. The World Health Organization estimates the annual incidence at about 1 million (Watt and Parola, 2003) with a case fatality rate of 30% if untreated (John et al., 2011).

Scrub typhus can occur in many different ecological environments. It is endemic in the tsutsugamushi triangle delimited by Japan, Australia, India, and Siberia. Scrub typhus can be manifested as a mild and self-limiting disease or as a severe, life-threatening multiorgan illness, depending on the infecting *Orientia* strain. The clinical picture comprises a typical eschar, lymphadenopathy, skin rash (macular or maculopapular or vesicular), fever, myalgia, headache, gastrointestinal symptoms, and cough. Early administration of adequate antibiotic therapy is essential to prevent an adverse outcome (Kelly et al., 2002; Attur et al., 2013).

Renal involvement has been thought to be uncommon in scrub typhus. In part, this has been due to inability to make an accurate diagnosis. Recent studies have suggested a higher prevalence of kidney involvement.

Urinary abnormalities, such as proteinuria, haematuria, and AKI are frequent in scrub typhus patients. In a prospective case record-based study of scrub typhus carried out in 259 patients in a tertiary hospital in South India, urinary abnormalities (proteinuria, haematuria, pyuria, and granular casts) were found in 147 patients (56.7%), and 60 patients (23.2%) developed AKI. In this study, all AKI patients had urinary abnormalities, 17 (28.3%) were oliguric, six (10%) needed haemodialysis, and two patients out of 259 died, both having AKI (Attur et al., 2013). In two studies from Taiwan, 8.3% and 6.6% of scrub typhus patients were noted to have AKI (Wu et al., 2009). In a couple of series from India the incidence of AKI was 19% and 42% (Kumar et al., 2012; Attur et al., 2013). All these studies used a single point measurement of antibody as a diagnostic test. However, the interpretation is doubtful because of the lack of population data on antibody prevalence. In a recent study (Kumar and Jha, unpublished data) that used nucleic-acid based test for diagnosis (Blacksell et al., 2012), renal involvement was seen in 52% of cases with proved infection. AKI was present in about 50%, and was a strong predictor of mortality. In a prospective study completed in a tertiary hospital in Southern India (Basu et al., 2011), AKI developed in 42.6% of 188 consecutive adult scrub typhus patients. In Indian children diagnosed with scrub typhus, the frequency of AKI ranged from 10% to 20% (Kumar et al., 2012; Palanivel et al., 2012).

Renal histology information in scrub typhus is limited with reports of acute tubular necrosis (ATN), acute tubulointerstitial nephritis, and mild mesangial hyperplasia (Allen and Spitz, 1945; Hsu et al., 1993; Chi et al., 1997; Kim et al., 2008). Complete renal recovery was described after doxycycline therapy (Yen et al., 2003).

The aetiopathogenesis of renal injury has been attributed to invasion and direct effects of the bacteria on renal tissue (Kim et al., 2008; Tseng et al., 2008), glucose-6-phosphate dehydrogenase deficiency-associated massive intravascular haemolysis (Raoult et al., 2004), rhabdomyolysis (Lee et al., 2003; Young et al., 2003), shock or hypovolaemia, and vasculitis (Attur et al., 2013).

The risk factors identified for scrub typhus-induced AKI development in univariate analysis were serum albumin < 3.0 g/dL (Lee et al., 2010), tachycardia, breathlessness, intensive care requirement, mechanical ventilation, thrombocytopenia, and serum creatine phosphokinase > 80 U/L (Attur et al., 2013). In multivariate analysis the independent risk factor associated with AKI development were delayed administration of doxycycline (Lee et al., 2008) and thrombocytopenia (Attur et al., 2013).

Management requires treatment with oral or intravenous doxycycline (100 mg twice daily for 7 days). Azithromycin and roxithromycin are also effective. Renal involvement shows rapid resolution following treatment. Mortality is high in those requiring dialysis and with multisystem involvement.

Haemorrhagic fever with renal syndrome is an important differential diagnosis of scrub typhus in areas where the two diseases are epidemic, such as Northern China. The early differentiation of these two diseases would allow adequate treatment to be started timely and so may be life-saving (Liu et al., 2007). Other important differential diagnoses for scrub typhus are malaria, typhoid fever, and leptospirosis (Nachega et al., 2007). The increment of worldwide outdoor touristic activities urges physicians to consider scrub typhus in the differential diagnosis of acute febrile diseases in travellers returning home from areas where the disease is endemic (Nachega et al., 2007; Vliegenthart-Jongbloed et al., 2013).

Tick typhus or the spotted fevers

Tick-borne rickettsioses are caused by bacteria from the spotted fever group (genus *Rickettsia*, family Rickettsiaceae, order Rickettsiales). The vectors for this zoonosis are ticks from the family Ixodidae. Humans are incidental hosts, since the bacteria usually do not infect humans during their natural cycle. Currently, at least 13 human vector-borne zoonoses are recognized to be caused by the spotted fever group rickettsiae. Because ecological characteristics of the tick acting as the vector influence the epidemiological and clinical aspects of these diseases, most of them are limited to specific geographic areas (Kelly et al., 2002; Parola et al., 2005). Renal abnormalities have been described in RMSF (Bradford et al., 1979; Walker and Mattern, 1979; Walker and Gear, 1985; Quigg et al., 1991; Conlon et al., 1996; Skhiri et al., 2004; Chen and Sexton, 2008; Channick et al., 2012), Mediterranean spotted fever (MSF) (Durrbach et al., 1996; Bellissima et al., 2001; Germanakis et al., 2006; Rovery and Raoult, 2008; Sousa et al., 2008; Saporito et al., 2010; Montasser et al., 2011; Nakamura et al., 2011), and more rarely in Japanese spotted fever (JSF) (Kodama et al., 2001; Wada et al., 2008; Nakamura et al., 2011) and Queensland tick typhus (Sexton et al., 1990; McBride et al., 2007).

RMSF is caused by *Rickettsia rickettsii* and is transmitted by the bite of infected hard ticks, which are the natural hosts and serve as both reservoirs and vectors for *R. rickettsii*. RMSF is the most severe of the spotted fever rickettsial diseases and causes significant morbidity and lethality, especially in the older and when adequate antibiotic is not given early in the course of the disease. RMSF occurs in North, Central and South America. The clinical picture is similar to other rickettsioses, with fever, malaise, nausea, vomit, abdominal pain, aching, chills, headache, myalgia, and arthralgia. The characteristic RMSF-induced cutaneous rash, frequently absent in the early phase of the disease, is pink and maculopapular, developing on the forearms, palms, soles, and legs (Kelly et al., 2002; Chen and Sexton, 2008).

Renal impairment is frequent in severe forms of RMSF (Chen and Sexton, 2008) and was reported in 19% of 114 RMSF patients (Conlon et al., 1996). Elevated serum creatinine at hospitalization and AKI were independent risk factors of mortality, whereas older age and low platelet count at presentation were associated with development of AKI (Conlon et al., 1996). Histology showed a variety of renal injuries, such as ATN, acute glomerulonephritis with inflammatory cell infiltration and subendothelial immune deposit, glomerular focal segmental tuft necrosis, and interstitial and vascular lymphocytic and/or mixed inflammation (Bradford et al., 1979; Walker and Mattern, 1979; Quigg et al., 1991). RMSF-induced renal injury has been attributed to hypotension, intravascular thrombosis, direct effects of *R rickettsii* on the endothelial cells and rhabdomyolysis (Bradford et al., 1979; Walker and Mattern, 1979; Chen and Sexton, 2008; Channick et al., 2012).

MSF, also known as 'boutonneuse fever', 'Indian tick typhus', 'Marseilles fever', and 'Kenya tick typhus', is caused by *Rickettsia conorii* and has the *Rhipicephalus sanguineus* ticks as vectors. MSF is endemic in the Mediterranean area, including northern Africa and southern Europe. With the large increase in ecotourism, imported cases of MSF have been reported in travellers returning from endemic to MSF-free areas. MSF presents with abrupt onset of high fever, flu-like symptomatology (headache, chills, arthralgia, and myalgia), maculopapular rash, and a typical black eschar (tache noire). This disease is usually benign, but severe forms may occur, with diffuse vasculitis and a clinical pattern similar to RMSF (Kelly et al., 2002; Rovery and Raoult, 2008).

Urinary abnormalities such as haematuria and proteinuria (Shaked et al., 1994; Germanakis et al., 2006), increase in serum creatinine (Shaked et al., 1994), and AKI (Shaked et al., 1994; Germanakis et al., 2006; Saporito et al., 2010; Montasser et al., 2011) have been reported in severe forms of the disease. A prospective study of 140 patients with *Rickettsia conorii* infection admitted to 13 Portuguese hospitals found that 57.7% of them had increased serum creatinine at hospitaliZation (Sousa et al., 2008). In this study, AKI was identified as a significant independent variable associated with fatal outcome (odds ratio 18.10). Renal histology of patients with MSF-associated renal injury has shown multifocal perivascular interstitial nephritis (Shaked et al., 1994), extracapillary glomerulonephritis (Durrbach et al., 1996; Skhiri et al., 2004), ATN (Skhiri et al., 2004), glomerular arteriolitis (Walker and Gear, 1985), and renal vascular and perivascular mononuclear cell inflammatory foci (Walker and Gear, 1985).

Renal injury in MSF has been attributed to dehydration, ischaemic tubular injury, direct action of *Rickettsia conorii* on renal tissue, and renal vasculitis (Walker and Gear, 1985; Skhiri et al., 2004; Montasser et al., 2011).

JSF is a tick-borne disease caused by *Rickettsia japonica*. Lethal cases are reported yearly in Southwest Japan. AKI has been reported in the context of multiple organ failure (Kodama et al., 2001; Wada et al., 2008). In a retrospective assessment of 51 patients with JSF, renal dysfunction was independently associated with development of disseminate intravascular coagulation and to more protracted illness duration (Nakamura et al., 2011).

Queensland tick typhus (QTT) is a tick-borne disease occurring in Australia, caused by *Rickettsia australi*, transmitted by the bite of *Ixodes holocyclus* or *I. tasmani* ticks, and considered as a relatively mild spotted fever. However, four cases of AKI related to QTT were described. Three patients survived and one died (Sexton et al., 1990; McBride et al., 2007).

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CHAPTER 194

Schistosomiasis

Rashad S. Barsoum

Introduction

Urinary system disease associated with schistosomiasis remained within the surgical domain for many decades, ever since the syndromes of lower urinary tract (LUT) involvement with *Schistosoma haematobium* were described by Egyptian pioneers during the early years of the last century (Badr, 1986). During the late 1960s, it was the Brazilian investigators' turn to draw attention to glomerular disease associated with *S. mansoni* infection (Andrade et al., 1971), which was confirmed later by Egyptian (Barsoum et al., 1977) and other African clinicians.

Lower urinary tract disease

Haematobiasis (*S. haematobium* infection) typically involves the bladder, lower ureters, seminal vesicles, and, less frequently, the vas deferens, prostate, and the female genital system. The initial lesions are mucosal granulomas which coalesce to form tubercles, nodules, or masses which usually ulcerate (Fig. 194.1). The surrounding mucosa is hyperaemic. The submucosa and muscle layers are also involved in the inflammatory process.

The characteristic clinical presentation is terminal haematuria, usually associated with increased frequency of micturition and dysuria. Diagnosis is made by finding the characteristic ova in the urine. Cystoscopic examination (Fig. 194.1), which is usually unnecessary in an endemic area, should show one or more of the mentioned lesions.

Chronic schistosomal morbidity is attributed to ageing granulomata with progressive fibrosis and calcification, the impact of which differs according to the anatomical site of affection.

Bladder

As the bladder lesions dry up, they leave a pale mucosa with patches of granular floor, descriptively known as 'sandy patches' which are characteristic of healed schistosomiasis (Fig. 194.1). These often calcify, leading to a typical linear opacity in a plain radiological examination (Fig. 194.2A). The lesions are patchy, the relatively healthy mucosa becomes encysted by the surrounding fibrosis, leading to a typical pathological picture known as 'cystitis cystica'. These healed lesions may be totally asymptomatic, though secondary bacterial infection usually supervenes due to urological instrumentation, leading to chronic cystitis. In certain endemic areas, *Salmonella* can cause resistant secondary bacterial cystitis (el-Din Hathout et al., 1967), owing to the known symbiotic association between schistosomes and certain *Salmonella* strains (Muniz-Junqueira et al., 2009).

Involvement of the submucosa may lead to contraction of the bladder capacity. Fibrosis of the muscle layer contributes to the bladder contraction, and may also lead to urodynamic disorders including an 'irritable', a 'hypertonic', or an 'atonic' bladder.

Bladder cancer is a common complication of urinary schistosomiasis (see Chapter 182). It is usually symptomatic, with increasing dysuria and frequency in a patient with chronic cystitis. Many patients pass necrotic tissue in the urine ('necroturia'), associated with agonizing pain and retention. The pain occurs during and following micturition, but may become persistent when the tumour spreads into the pelvic tissues or infiltrates the adjacent nerves. The neoplasm may appear as a crater in the calcified bladder wall on a plain pelvic radiogram and as an ulcer or irregular filling defect in a cystogram (Figure 194.2C). The tumour can be seen on cystoscopy (Fig. 194.1). Urine cytology may be misleading owing to the mucosal metaplasia as a result of chronic inflammation.

Urethra

The bladder outlet is one of the favourite sites for deposition of eggs, and leads to intense fibrosis that induces a bladder neck obstruction. This, in combination with detrusor dysfunction may lead to chronic retention. Incontinence may develop, especially as a complication following urological procedures intended to dilate the bladder neck.

Urethral lesions may extend beyond the bladder neck, leading to strictures or fistulae, which again are usually iatrogenic, resulting from instrumentation rather than the disease.

Ureterovesical junctions

Being at the base of the bladder trigone, the ureterovesical junction is particularly vulnerable to dense schistosomal lesions. During the initial phase of the disease, it often becomes congested and oedematous, which may lead to configurational changes causing functional obstruction or reflux. These consequences may lead to transient back pressure changes in the upper urinary tract, which are typically reversed by anti-schistosomal treatment. Persistent changes are usually iatrogenic, due to urological procedures as cystoscopic dilatation, surgical incision, or ureterovesical implantation.

Ureters

Bilharzial lesions are typically limited to the lower halves of the ureters, corresponding to the part below the lower border of the third lumbar vertebra. This has been attributed to anastomotic channels at this site, in between the inferior mesenteric and the periureteric and perivesical veins. These communications are believed to be the main route through which *S. haematobium* worms migrate to the urinary system.

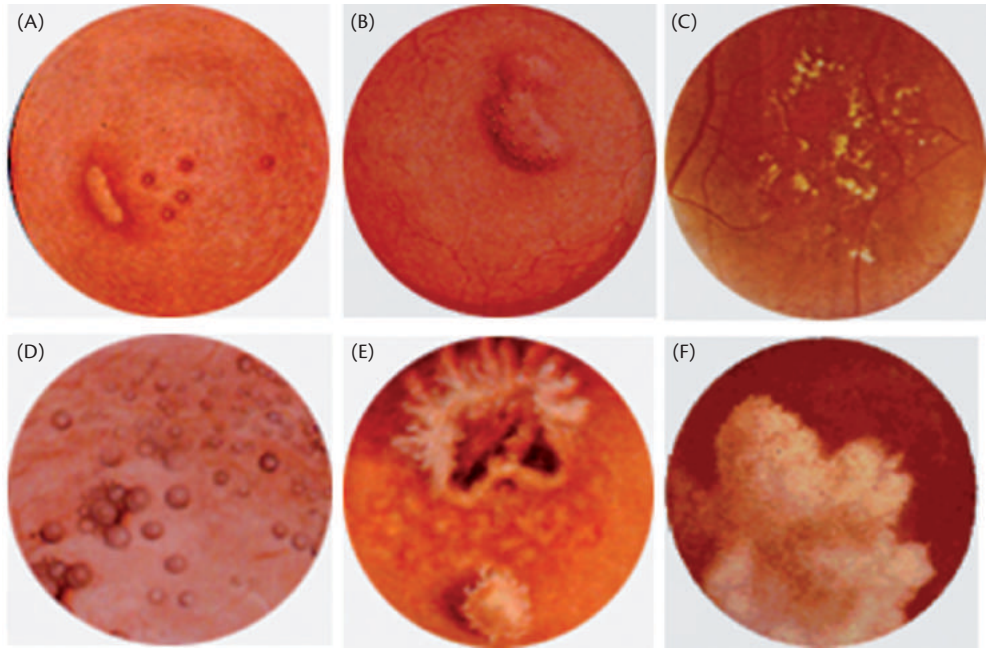

Fig. 194.1 Cystoscopic appearances of common bilharzial lesions in the urinary bladder. (A) Bilharzial pseudotubercles and adjacent ulcer. (B) Bilharzial sessile mass covered by pseudotubercles. (C) Sandy patches. (D) Cystitis cystica. (E) Malignant ulcer (squamous cell carcinoma) with adjacent phosphate encrustations and sandy patches. (F) Fungating malignant mass (transitional cell carcinoma).

The lower ureteric lesions in schistosomiasis mirror those in the bladder, including the early tubercles and ulcers, and subsequently the sandy patches and cysts, known here as 'ureteritis cystica'. Fibrosis of the lower ureteric musculosa may lead to partial obstruction. The upper ureter exhibits compensatory dilatation and hypertrophy that generates enough bolus pressure to overcome the distal obstruction, thereby protecting the kidneys from back pressure.

Genital structures

Inflammatory lesions and fibrosis may develop in the seminal vesicles and prostate in males, and the uterine cervix, vagina, and vulva in females. Most of these lesions are asymptomatic, though the subsequent fibrosis may lead to sterility in men. Calcification of the seminal vesicles is one of the characteristic radiological signs in schistosomiasis.

Upper urinary tract disease

Obstructive nephropathy

Back pressure effects may extend to the kidneys in those with failure of ureteric urodynamic compensation, or those with vesicoureteric reflux (Fig. 194.2B). As with obstructive nephropathy

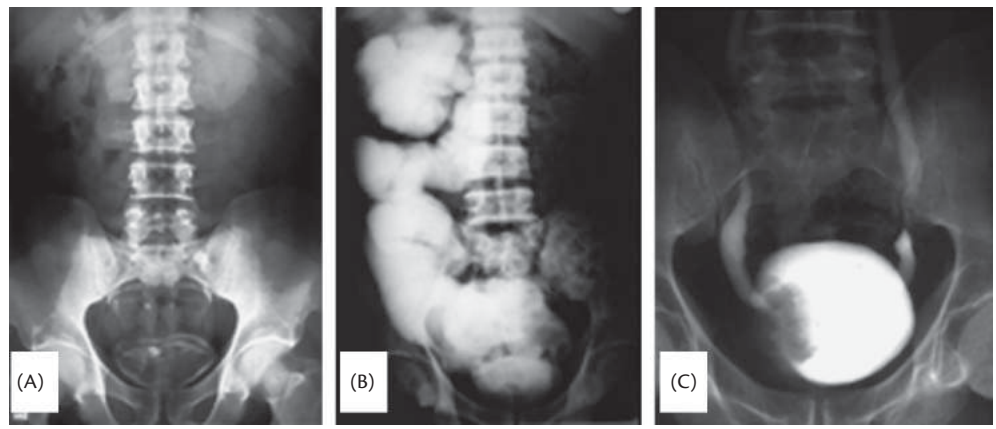

Fig. 194.2 Radiological appearances in urinary schistosomiasis. (A) Plain radiographic appearances of the urinary tract. Note the linear bladder calcifications. (B) Ascending urogram showing a contracted bladder with right grade V vesicoureteric reflux, megaureter, and hydronephrosis with loss of renal parenchyma. (C) Ascending cystogram showing a large irregular filling defect in the bladder due to a fungating malignant tumour.

due to other causes, ascending infection further complicates the scenario.

It is noteworthy that, owing to the associated fibrosis of renal parenchyma, relief of obstruction may not correct the back pressure appearances. In these cases, pressure measurements are necessary to avoid unnecessary or even harmful intervention. The gold standard procedure here is the Whitaker test, which correlates with the isotopic diuretic renogram in about 75% of cases.

Chronic pyelonephritis

A combination of obstruction, reflux, infection, and possibly parasite-specific immune-mediated tubular injury (Abdel-Rahman et al., 1994) leads to chronic interstitial nephritis. Loss of concentrating ability, sodium wasting, and tubular acidosis constitute a typical early triad. Although urinary calcium excretion is increased due to associated bone resorption, and citrate concentration is reduced due to tubular acidosis, stone formation is unusual owing to the associated polyuria. However, the incidence of infective stones is increased in schistosomiasis.

The glomeruli may show 'alternative' changes associated with periglomerular fibrosis or concomitant immunological damage (see later). Eventually, glomerular function declines, ending with renal failure. As with other end-stage renal diseases due to chronic interstitial disease, anaemia, acidosis, and bone disease.

Glomerulonephritis

Schistosoma-associated glomerulonephritis (SAG) has been reported from Africa (Egypt, Sudan, Algeria, Nigeria, Madagascar) and Latin America (Brazil, Peru, Costa Rica). According to autopsy reports (Rocha et al., 1976) and clinical studies (Andrade and Rocha, 1979; Barsoum, 1993), 12–15% of patients with hepatosplenic schistosomiasis develop glomerular lesions. This relative frequency has not changed over the years (Rodrigues et al., 2010), though its epidemiological impact has regressed owing to the decline in the overall prevalence of schistosomiasis (Correia et al., 1997). The role of schistosomiasis in the pathogenesis of 'steroid-resistant' nephrotic syndrome in black Africa remains controversial.

Clinically, the disease is encountered as occult, overt, or end-stage glomerulopathy. Among the factors that define the severity of glomerular lesions are species and strains of the parasite, associated infections, racial and genetic host factors (Barsoum, 1987), and the extent of associated hepatic involvement (Barsoum et al., 1988).

Six distinct clinicopathological patterns are identified (Fig. 194.3).

Class I is essentially a subclinical form of SAG, reported in asymptomatic patients with *S. haematobium* (Soliman et al., 1987), or *S. mansoni* (Sobh et al., 1988a) infection. Microalbuminuria may be the only indicator of kidney disease at this stage (Amin et al., 1993). Histology shows focal or diffuse mesangioproliferative glomerulonephritis, and immunoglobulin (Ig)-M and C3 deposits are detectable on immunofluorescence. Schistosomal gut antigen deposits have been most often reported with this lesion. Mesangial immune complex deposits are seen by electron microscopy (Sobh et al., 1988a).

Class II is an acute expression of SAG, almost exclusively encountered in patients with hepatosplenic schistosomiasis and concomitant *Salmonella* infection (Bassily et al., 1976; Martinelli et al., 1992). Such patients are severely ill, pyrexial, and anaemic. Their hair becomes brittle, thin, and depigmented. They develop a characteristic skin rash, mainly on the flexor surfaces of the forearms and the front of the chest and abdomen. The spleen is moderately enlarged, soft, and tender. Acute-onset nephrotic syndrome is characteristic, with gross proteinuria and severe hypoalbuminaemia. Serum immunoglobulins exhibit a polyclonal response, leading to false-positive serological tests of syphilis, and rheumatoid factor in 5–10% of patients. There is a considerable increase in alpha-1 globulins, indicating the role of bacterial infection. In addition there is a modest increase in serum alpha-2 and beta globulins typical of the nephrotic syndrome. Serum cholesterol is often normal or even low as a result of the associated hepatic dysfunction. *Salmonella* can be

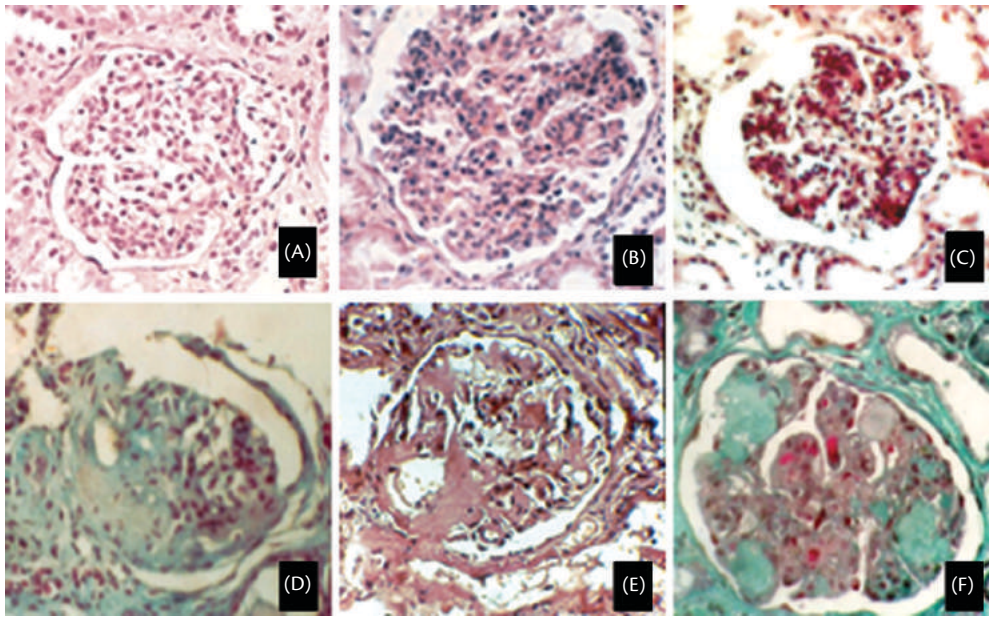

Fig. 194.3 Histological patterns of schistosomal glomerular lesions. Classes I to VI in sequence from A to F (explanation in text).

recovered by bone-marrow cultures, and less frequently by blood or urine cultures. Serum level of C3 is consistently reduced with evidence of alternative-pathway activation.

Renal biopsy shows a large number of transit cells, including monocytes and neutrophils, in addition to the mesangial proliferation. The consistent feature on immunofluorescence is the subendothelial finely granular deposition of complement and mesangial IgG.

Classes III and *IV* are the classical overt chronic syndromes of SAG. Their clinical presentations are similar but the histopathological patterns are different, being mesangiocapillary (membranoproliferative) and focal segmental sclerosis respectively. Class III is encountered mainly in Caucasians, while class IV is more frequent in black patients, even in the same community (Lopes et al., 2002).

Class III lesions are consistent with either type I or type III mesangiocapillary glomerulonephritis. Mesangial, subendothelial, and/or subepithelial deposits of IgG, IgA, IgM, C3, and fibrin are seen. Schistosomal antigens are usually not detected. Electron microscopy confirms the presence and localization of immune complex deposits.

Class IV lesions may be categorized under the 'cellular variant' of focal and segmental sclerosis. Immunofluorescence shows non-specific mesangial immunoglobulin deposits and, interestingly, IgA in the sclerotic lesions (Barsoum et al., 1996). Schistosomal antigens are typically not detected.

Both patterns are usually seen with *S. mansoni* infections, and rarely with *S. haematobium* (Ezzat et al., 1978). Almost all patients have hepatosplenic disease. The crucial role of hepatic fibrosis has been documented in several animal models, postmortem observations (Rocha et al., 1976), and clinical studies (Andrade et al., 1971). The associated impairment of hepatic macrophage function (Barsoum et al., 1988) and portosystemic shunts seem to permit a large load of schistosomal gut antigens, as well as IgA, to escape normal hepatic clearance.

There is evidence that excess IgA in schistosomal hepatic fibrosis is not entirely attributed to impaired clearance. The selective increase in circulating anti-gliadin IgA (Barsoum et al., 1996) suggests increased synthesis in the gut mucosa, presumably in response to the deposited ova. More recent observations suggest that the B lymphocytes preferentially synthesize IgA at the expense of IgM in patients with chronic schistosomal infection (Béniguel et al., 2003). This switching seems to occur under the influence of interleukin (IL)-10 (Flores-Villanueva et al., 1996), which supervenes in late stages of the schistosomal life cycle in humans.

Stage III/IV SAG may be discovered accidentally by finding mild to moderate proteinuria with an increase in the urinary red cells and casts. More advanced cases develop a frank nephrotic syndrome, with gross unselective proteinuria and a rich urinary sediment. Hypertension is present in about 30% of patients. Usually, there is mild to moderate anaemia, which is attributed to associated nutritional deficiency and other parasitic infestations, in addition to reduction of the renal mass.

Other findings include a firm and shrunken liver, splenomegaly, and ascites. Hypoalbuminaemia is severe and hyperlipidaemia is unusual. There is a polyclonal increase in gamma globulins, with considerable increase of serum IgG and less frequently IgA. Serum complement is usually normal.

Progression to end-stage renal disease has been documented in several studies (Brito et al., 1970; Sobh et al., 1987). As with other renal diseases, poor prognostic markers include gross proteinuria, hypertension, and rapid functional deterioration. Histopathological parameters of poor prognosis include glomerular sclerosis, crescents, adhesions, and advanced tubulointerstitial lesions.

Class V includes patients with amyloid deposits among other *Schistosoma*-associated renal lesions. The epidemiological significance of this class is suggested by the threefold increase in the incidence of renal amyloidosis among *Schistosoma*-infected subjects in endemic areas. In one series, amyloid deposits were detected in as many as 15% of renal biopsies obtained from patients with schistosomal glomerulopathy (Barsoum et al., 1979).

There is no correlation between the incidence of such lesions and the duration of either infection or renal disease. The usual presentation is nephrotic syndrome. Hypertension is encountered in 10–15% of patients. The kidneys are enlarged in 25% of cases.

Class VI is the most recently described lesion encountered in a subset of patients who have evidence of both schistosomal and hepatitis C virus infection. Patients typically present with hepatosplenic disease, vasculitic skin rash mainly in the lower extremities, and often arthralgia and myalgia (Meltzer's triad) (Barsoum, 2004). In these patients, serum C4 is typically very low or even undetectable, reflecting the supervening cryoglobulinaemia. C3 may also be consumed as a part of the activated complement system. Rheumatoid factor is typically positive in high titres, reflecting the highly activated B-lymphocyte clones, typical of chronic hepatitis C virus (HCV) infection. Renal histology shows mixed glomerular lesions of SAG as well as cryoglobulinaemic HCV nephropathy, characterized by mesangiocapillary (membranoproliferative) lesions, hyaline thrombi, necrotizing lesions, as well as amyloid deposits (Fig. 194.3F).

Treatment

Lower urinary tract

Early schistosomal lesions of the lower urinary tract respond to antiparasitic treatment (see Chapter 182), leading to healing of bladder lesions and relief of functional ureterovesical obstruction.

Associated bacterial cystitis requires prolonged chemotherapy with oral agents such as nitrofurantoin or co-trimoxazole. *Salmonella* infection responds to monotherapy with quinolones or dual treatment with ampicillin and co-trimoxazole.

Stenotic or regurgitant lesions of the ureterovesical junction should be handled carefully, since many of the serious sequelae are attributed to unnecessary intervention. Appropriate endoscopic or surgical treatment can, however, correct obstructive lesions and intercept the development of renal failure.

Upper urinary tract

Apart from the relief of obstruction and control of secondary bacterial infection, little can be done for the sequelae of schistosomiasis in the upper urinary tract.

Schistosomal glomerulopathy

The effect of treatment on SAG is debatable. Regression of proteinuria has been sporadically reported following the administration of parasiticidal agents (Ott et al., 1983), corticosteroids (Pyrrho Ados et al., 2002), or ciclosporin (Elkerdany et al., 1998). Case–control studies, however, have not confirmed these observations (Sobh

et al., 1988b; Martinelli et al., 1989). A notable exception is the response of class II disease to combined antischistosomal and antibacterial treatment (Bassily et al., 1976). Complete recovery is expected in 6–8 weeks.

No adequate data is available on the progress of renal amyloidosis after effective antischistosomal chemotherapy. Improvement (Omer and Wahab, 1976) or stabilization (Barsoum et al., 1979) has been described in different reports. Colchicine is known to prevent the development of amyloidosis when used in conjunction with praziquantel in Syrian Golden Hamsters (Sobh et al., 1995). However, there is no evidence of clinical benefit of this treatment in humans.

Renal replacement therapy

Dialysis

Special problems are encountered in patients with hepatosplenic schistosomiasis, who may have oesophageal or gastric varices and/or ascites. These are particularly risky candidates for peritoneal dialysis, owing to the excessive loss of protein, as well as for haemodialysis, owing to the need for anticoagulation. In our experience, it was possible to achieve a 1-year survival of 67% in those treated by haemodialysis following prophylactic sclerotherapy of their varices (unpublished data).

Transplantation

The overall results of renal transplantation in patients with healed schistosomal lesions are not different from those with other renal disorders (Mahmoud et al., 2001). However, gross bladder fibrosis may lead to a greater incidence of surgical complications, mainly urinary fistulas, during the early postoperative period (Shokeir, 2001). Pretransplant intervention may be needed for correction of disturbed bladder urodynamics or cure of persistent infection. The latter frequently necessitates bilateral nephrectomy.

Uncomplicated residual hepatic fibrosis in the recipient does not seem to significantly modify the pharmacokinetics of the immunosuppressive agents used in transplanted patients. However, variations in ciclosporin blood levels have been noticed by certain groups (El-Agroudy et al., 2008) and attributed to altered absorption of the drug.

Recurrence of schistosomal lesions has been documented after renal transplantation (Mudawi et al., 2006) including glomerulopathy in a few (Azevedo et al., 1987), suggesting resumed fecundity and antigen release from living worms. Re-infection with *S. haematobium,* without evidence of recurrence of glomerular pathology, has also been described in patients living in endemic area (Mahmoud et al., 2001). In view of these observations, prophylactic antischistosomal chemotherapy has been recommended for recipients known to have been previously infected with the parasite.

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CHAPTER 195

Nematode infections

Raja Ramachandran and Vivekanand Jha

Introduction

Filarial worms and their larvae are parasitic round nematodes encountered in the tropics and cause a group of diseases called filariasis. Filarial nematodes are transmitted to humans by arthropods, usually mosquitoes, carrying the larvae. After release into human circulation, they circulate as microfilariae, migrate to tissues, and develop into adult worms where they live for years. Clinical disease develops only after repeated, prolonged infection. Presentation depends upon the niche occupied by the worm in the human body. Lymphatic filariasis, caused by *Wuchereria bancrofti, Brugia malayi*, and *Brugia timori*, is encountered in Asia, Africa, parts of South America, and the Caribbean. Adult worms reside in and block the lymph node sinuses, and lead to elephantiasis characterized by woody oedema of the draining area. Death of the worms leads to intense granulomatous reaction causing further obliteration of the lymphatics. Subcutaneous filariasis is caused by *Loa loa, Mansonella streptocerca*, and *Onchocerca volvulus*. All three are encountered in equatorial Africa, *O. volvulus* is also seen in parts of South America. These organisms occupy the subcutaneous layer of skin and conjunctiva. Onchocerciasis primarily affects the skin, eyes, and lymph nodes and causes subcutaneous nodules, fibrosis, and corneal opacities leading to loss of vision (river blindness). Similarly, loiasis is characterized by attacks of angio-oedema and cutaneous erythema (Calabar swellings) and subconjunctival injection secondary to migration of the worm. Serous cavity filariasis is caused by *Mansonella perstans* and *Mansonella ozzardi.* These organisms infect the serous cavities—pleural, pericardial, and peritoneal—as well as the mesentery and retroperitoneum. Presentation is with constitutional symptoms, cutaneous erythematous swellings, and evidence of serositis.

Of the eight filarial species, association between filariasis and glomerular disease are reported with *Loa loa, Wuchereria bancrofti, Onchocerca volvulus*, and *Brugia malayi* (Pillay et al., 1973; Chugh et al., 1978; Date et al., 1979).

Clinical features

The exact incidence of renal involvement in filarial infections is very difficult to estimate. Asymptomatic urinary abnormalities are reported in 11–25% of patients with onchocerciasis and loiasis. Nephrotic syndrome is seen in 3–5% of cases and is described more commonly in those with polyarthritis and chorioretinitis (Hall et al., 2001). Renal function impairment is rare and is reported in an exceptional case of onchocerciasis-associated glomerulonephritis. Proteinuria and/or haematuria have been reported in 50% of patients with lymphatic filariasis. Twenty-five per cent showed glomerular proteinuria (Dreyer et al., 1992). Proteinuria, microhaematuria, and hypertension are more common in patients with obstructive disease compared to filarial fever or microfilaraemia.

Another presentation of lymphatic filariasis is with chyluria (milky urine). Renal lymphatics follow the renal vein and end in the lateral aortic glands; efferents from lateral aortic glands form the lumbar trunks. These, together with the intestinal trunks, drain into the cisterna chylii. Increased pressure in the cisterna chylii or the intestinal trunk leads to varicosity and rupture that with resultant regurgitation of chyle into renal calyces or pelvis (Singh et al., 2008). Patients with filariasis with chyluria can have nephrotic range proteinuria with no obvious glomerular lesions (Tanaka et al., 2012).

False-positive anti-dsDNA, rheumatoid factor (immunoglobulin (Ig)-G and IgM), and autoantibodies against various cytoplasmic proteins have been noted in patients with filariasis and glomerular involvement. Two-thirds of the patients with nephrotic syndrome and 38% of patients with nephritic syndrome in filarial endemic regions exhibit antibodies to microfilarial antigen by enzyme-linked immunosorbent assay (Chaturvedi et al., 1995).

Pathology

Several patterns of glomerular pathology are described with filarial nephropathy and include minimal change disease, collapsing focal segmental glomerulosclerosis, mesangiocapillary, and diffuse and mesangioproliferative glomerulonephritides (Pakasa et al., 1997). A diffuse thickening of glomerular basement membrane with endocapillary proliferation is the commonest finding. Infiltrating eosinophils and few crescents may be noted. Microfilaria may be demonstrated in arterioles, glomerular, and peritubular capillaries (Pakasa et al., 1997). Immunofluorescence shows IgG, IgM, and C3 in mesangium and along capillary loops. *O. volvulus* and *B. malayi* antigens have been demonstrated in a significant proportion of biopsies. Ultrastructural examination shows podocyte effacement and electron dense deposits in subepithelial, subendothelial, and intramembranous locations (Ormerod et al., 1983).

Pathogenesis

Immune mechanisms play major roles in filarial glomerulonephritis. The circulating immune complex levels correlate with adult worm burden (Katner et al., 1984; Nakagaki et al., 1990). Ultrastructural alteration of anionic sites in the glomerular basement membrane was studied in four dogs infected with *Dirofilaria*

immitis and two normal control dogs using polyethyleneimine. The sites were distributed irregularly in the thickened lamina densa in the glomeruli of the infected dogs, whereas it was normal in uninfected controls. Paradoxically, treatment with antifilarial drugs like diethylcarbamazine (DEC) or ivermectin may lead to antigen release from the dead worms and exacerbate the immune process (Ngu et al., 1980; Langhammer et al., 1997).

Treatment

Patients with subnephrotic range proteinuria respond well to DEC therapy. However, patients with nephritic and nephrotic syndrome at presentation show variable results. Therapeutic apheresis has been tried prior to DEC initiation to remove the microfilaria and prevent treatment-induced antigen release (Abel et al., 1986). There is no role for steroids and/or immunosuppressive therapy.

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CHAPTER 196

Mycobacterial infections: tuberculosis

John Eastwood, Cathy Corbishley, and John Grange

The genus *Mycobacterium*

The principal characteristic of members of the genus *Mycobacterium* is their elaborate lipid-rich cell walls which impart the property of acid-fastness; namely, the ability to retain colouring by arylmethane dyes after wash with dilute mineral acids.

The genus contains two major pathogens, the *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*. The former contains several named species (Table 196.1), although they are really variants of a single species. These variants have evolved from a common progenitor, closely resembling *M. canetti*, by the successive loss of units of DNA. In addition, a number of lineages or families of differing virulence have been described within *M. tuberculosis*. The tuberculosis vaccine, bacillus Calmette–Guérin (BCG), which is sometimes used intravesically in the treatment of superficial bladder cancer, can lead to the development of renal lesions (Lamm, 1992) and, rarely, acute kidney injury due to interstitial nephritis (Manzanera Escribano et al., 2007).

Some mycobateria are found around water sources marshes, mud, ponds, lakes, rivers, and estuaries, and dubbed environmental mycobacteria (EM). (Collins et al., 1984). Some species colonize water pipes and may contaminate water used for washing and bathing. Accordingly, they may contaminate the lower urethra and external genitalia so great care is required in interpreting the microscopy of acid-fast bacilli in, and cultures of EM from, urine. Likewise, collection of urine into non-sterile containers has led to misdiagnosis of urinary tract infection by EM (Collins et al., 1984).

There are two groups of EM, the rapid and slow growers. The most commonly encountered in clinical practice are listed in Table 196.1. Most of those encountered as pathogens are slow growing, although among the rapid growers *Mycobacterium chelonae, M. abscessus*, and *M. fortuitum* are well-recognized pathogens. The most frequently encountered slow-growing opportunist pathogens are members of the *M. avium* complex (MAC); human disease is usually due to *M. avium* subspecies *hominissuis* or subspecies *intracellulare*. Members of MAC are a common cause of opportunist infection in patients with AIDS although there has been a fall in the number of cases in developed countries since the introduction of highly active antiretroviral therapy.

Epidemiology

Tuberculosis has a worldwide distribution (Fig. 196.1). Skin testing surveys have shown that one-third of the world's population, approximately 2000 million people, have been infected by tubercle bacilli and that approximately 1% of the population is newly infected each year. The disease is principally transmitted by those with cavitating post-primary pulmonary tuberculosis. The number of people infected by a source case depends on many factors including overcrowding and ventilation; on average, an untreated source case infects 10–15 people a year. Children with primary tuberculosis, however, are rarely infectious. Primary skin lesions are the result of traumatic inoculation. *M. bovis* infection may be acquired by drinking contaminated milk.

Only a minority of infected people develops active tuberculosis. About 5% of those infected develop primary tuberculosis within 3 years and a further 5% post-primary tuberculosis later in life: a total risk of 10%. The majority of cases of post-primary tuberculosis are the result of endogenous reactivation but DNA fingerprinting shows that exogenous re-infection also occurs.

In 2011, there were an estimated 8.7 million new cases of tuberculosis worldwide, 14 million prevalent cases, and 1.4 million deaths of whom around 0.4 million were co-infected with HIV (World Health Organization (WHO), 2012). The majority of cases, 85%, were in South-East Asia, the Western Pacific region, and Africa. Around 13% of new cases are co-infected with HIV, with 80% of these living in sub-Saharan Africa.

The widespread adoption of the WHO tuberculosis control strategies has led to a reduction in the incidence of tuberculosis in many regions, even in those with a high burden of HIV infection, and the mortality has shown a 41% reduction since 1990 (WHO, 2012). The risk of a person co-infected with the tubercle bacillus and HIV developing tuberculosis is around 20 times greater than that of someone without HIV. The risk of a person with AIDS developing tuberculosis after exposure to a source case is extremely high, approaching 100%. Also, the progress of the disease is very rapid—severe and widespread tuberculosis may develop within a few months of infection.

A major problem in tuberculosis control is the emergence of drug resistance, particularly multidrug resistance (MDR-TB), defined as resistance to at least rifampicin and isoniazid. In 2011, there were almost 60,000 MDR-TB notifications, with particularly high incidences in China, India, the Russian Federation, and South Africa but this is probably only a fifth of the actual numbers (WHO, 2012). An additional major problem is the emergence of extensively drug-resistant tuberculosis (XDR-TB), defined as MDR-TB with additional resistance to a quinolone and an injectable second-line

Table 196.1 The principal mycobacterial species encountered in clinical practice

1. Members of the *Mycobacterium tuberculosis* complex	
M. tuberculosis	The human tubercle bacillus
M. bovis	The bovine tubercle bacillus but also a cause of human disease. The vaccine strain, bacillus Calmette–Guérin (BCG) is derived from *Mycobacterium bovis*
M. caprae	Closely related to *M. bovis*, a cause of disease in goats and, occasionally, in human beings
M. africanum	A heterogeneous group of strains mostly isolated from human beings in Equatorial Africa
M. microti	A cause of tuberculosis in small mammals such as the vole but, with very rare exceptions, avirulent in human beings
M. pinnepedii	A cause of disease in seals and sea lions and, very rarely, in humans occupationally exposed to them
M. canetti	A rare and primitive variant forming smooth colonies on culture media
2. The leprosy bacillus, *M. leprae*	
3. The most frequently encountered environmental mycobacteria in clinical material	
M. abscessus	A rapid grower, formerly a variant of *M. chelonae* which it closely resembles
M. avium	The *M. avium* complex contains several subspecies, with most cases of human disease being due to subspecies *avium*, *intracellulare* and *hominssuis*
M. celatum	Principally a pulmonary pathogen
M. chelonae	A rapid grower. An occasional cause of disseminated disease in renal transplant patients and the most common cause of mycobacterial peritonitis in CAPD patients
M. fortuitum	A rapid grower. An occasional cause of peritonitis in CAPD patients
M. gordonae	A common isolate from water (hence the old name *M. aquae*). A frequent contaminant of urine. A very cause of pulmonary disease
M. haemophilum	An occasional cause of skin lesions in renal transplant patients
M. kansasii	Principally a pulmonary pathogen
M. malomense	A species isolated with increasing frequency in Europe. Principally a pulmonary pathogen
M. marinum	Found in water and as the cause of cutaneous granulomas (swimming pool or fish tank granuloma). A rare cause of disseminated disease in immunosuppressed patients
M. peregrinum	A rapid grower, formerly a variant of *M. fortuitum*
M. scrofulaceum	A cause of cervical lymphadenopathy (scrofula) and, occasionally, lung disease
M. simiae	Principally a pulmonary pathogen
M. szulgai	Principally a pulmonary pathogen
M. ulcerans	The cause of Buruli ulcer, characterized by large undermined skin ulcers and occurring in several tropical countries
M. xenopi	Of limited geographic distribution. A frequent contaminant of urine in South England

drug. The global prevalence of XDR-TB is uncertain owing to a lack of suitable laboratories in many countries but by 2011 at least one case had been reported in 84 countries with the average proportion of MDR-TB cases with extensive drug resistance being 9% (WHO, 2012). Genitourinary tuberculosis is widely under-diagnosed and under-notified. An analysis of 13,634 cases of non-pulmonary tuberculosis aggregated from five studies in the United States and United Kingdom showed that genitourinary disease accounted for 27%. It was thus the second most frequent form of non-pulmonary tuberculosis after tuberculous lymphadenopathy (32%) (Kennedy, 1989). In 2009, however, 118 of 8698 cases of tuberculosis in the United Kingdom (1.3%) were genitourinary, being exceeded in frequency by gastrointestinal (4.1%), spinal (4.1%), disseminated (2.9%), other bony (2.0%), and meningeal/central nervous system (1.3%) (Health Protection Agency Centre for Infections, 2010). The reason for the difference between the two studies is unclear but may be explained by differing notification practices.

Review of the genitourinary tuberculosis literature shows that, in contrast to other forms of non-pulmonary tuberculosis, it is twice as common in men as in women, the mean age is 40.7 years (range 5–90 years), in 26.9% of cases one kidney is non-functional, and 7.4% of patients have a reduced glomerular filtration rate (GFR) (Figueiredo et al., 2008). Among haemodialysis patients, however, tuberculosis is commoner in women (Christopoulos et al., 2009a).

The relative incidence of genitourinary tuberculosis also varies within countries. Reports from developed countries show a higher incidence of non-pulmonary tuberculosis in ethnic minority groups (Ormerod, 1993). A survey in south-eastern England showed that extrapulmonary forms of tuberculosis were more common in patients of Indian origin than in ethnic Europeans but that genitourinary disease occurred less frequently (Table 196.2). This may perhaps be attributed to different age distributions in the two groups (Grange et al., 1995).

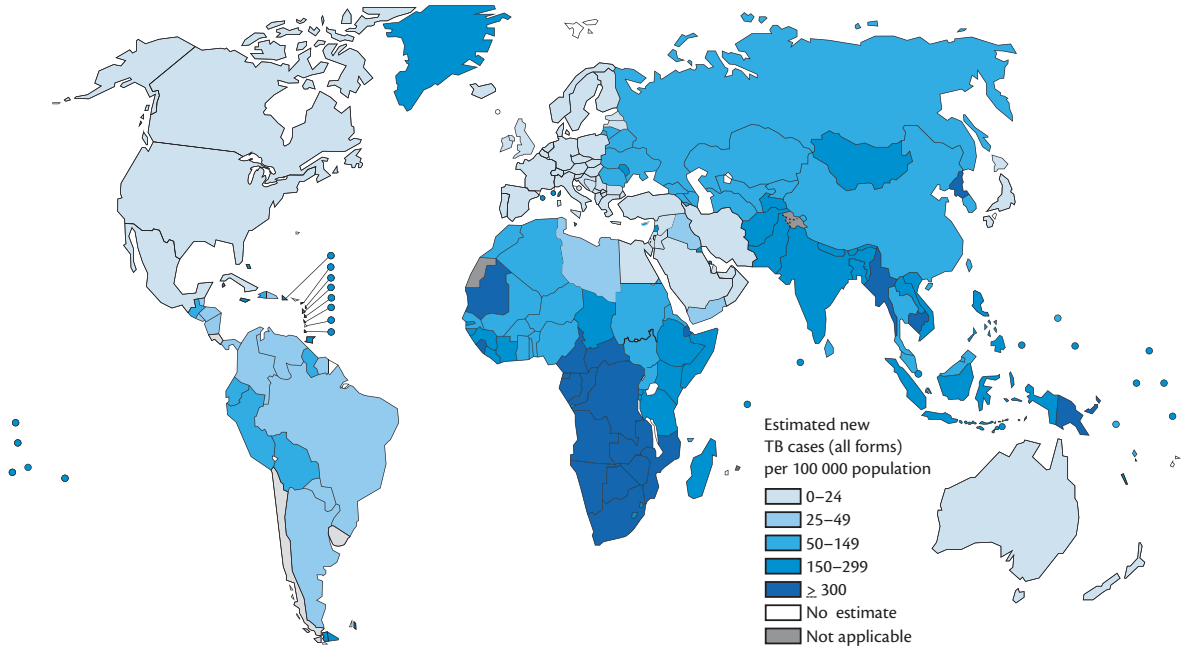

Fig. 196.1 Estimated tuberculosis incidence rates, 2011.
Reproduced from WHO (2012) with permission.

Tuberculosis due to *M. bovis* is now rare in developed nations and most cases occur in the elderly as a result of reactivation of dormant infection acquired before the disease had been controlled in cattle. Between 1977 and 1988, a quarter of all cases of *M. bovis* tuberculosis in south-eastern England involved the genitourinary system (Yates and Grange, 1988). This is relevant to tuberculosis control in cattle because farm workers with genitourinary tuberculosis due to *M. bovis* have infected cattle by urinating in cowsheds: one worker infected 48 cows in four different herds (Schliesser, 1974).

Table 196.2 Non-pulmonary tuberculosis in indigenous European and Indian subcontinent ethnic groups in South-East England—1977–1991[a]

	European		Indian subcontinent	
	1977–83	1984–91	1977–83	1984–91
	%	%	%	%
Genitourinary	37.6	27.2	6.8	8.4
Lymphadenopathy	30.3	36.6	55.6	59.6
Bone and joint	19.5	19.7	24.7	19.2
Abdomen	5.1	7.8	7.8	8.3
Central nervous system	6.7	4.4	4.3	3.7
Disseminated	0.8	4.2[b]	0.7	0.6
Total individuals	1470	861	1914	1794
Non-pulmonary as % of all cases of tuberculosis	21.3	18.9	49.5	45.1

[a]Data from Grange and Yates (1993).

[b]Increase in disseminated disease in this group relates to emergence of HIV.

Pathogenesis

The primary site of infection by the tubercle bacillus is usually the lung with involvement of the hilar lymph nodes. Some bacilli are disseminated further via the bloodstream and lodge in distant structures. In immunocompetent individuals, about 95% of primary infections resolve with no symptoms.

Primary tuberculosis usually develops within 3 years of infection (Wallgren, 1948) but renal tuberculosis is an exception and often only develops after 8 or more years (Ustvedt, 1947). Occasionally, a tuberculous lesion erodes the wall of a major blood vessel and large numbers of bacilli are released into the bloodstream leading to miliary tuberculosis, which is characterized by the development of millet-seed-like granulomas throughout the body including the kidney.

Primary tuberculous lesions, whether self-limiting or progressive, result in the development of tuberculin reactivity within 3–10 weeks of infection. About 5% of infected tuberculin positive people eventually develop post-primary tuberculosis. Post-primary tuberculosis is either the result of reactivation of dormant foci of infection, or of exogenous re-infection.

Granulomas resulting from the implantation of tubercle bacilli in the kidney during haematogenous dissemination following primary infection appear first near glomeruli, probably relatively high oxygen tension. These cortical granulomas, often bilateral, can remain dormant for many years. In some cases as yet unknown factors allow the bacilli to proliferate. If this happens, the enlarging granulomas rupture into the proximal tubule and live bacilli reach the loop of Henle where they survive on account of impaired phagocytosis in the hypertonic environment. Granulomas can then develop in the medulla, a process sometimes sufficiently destructive to cause papillary necrosis with rupture into the pelvicalyceal system. Bacilli can then enter the renal pelvis, ureters, bladder, prostate, and epididymis. Bacilli can also reach these structures

by dissemination via the local lymphatics, or by direct haematogenous spread.

Clinical manifestations

'Classical' urinary tract tuberculosis

Urinary tract tuberculosis is a relatively late manifestation of disease. In developed nations, it typically presents in the fourth to sixth decade (Kennedy, 1989), and in an insidious manner. It is therefore easily overlooked.

There may be lower urinary symptoms typical of infection yet routine urine culture will be sterile. The finding of significant numbers of white blood cells yet negative culture (Box 196.1) in a patient with urinary tract symptoms should alert the clinician to the possibility of tuberculosis of the urinary tract (Chiang et al., 2010; Dhua et al., 2011), including those infected with HIV (Nourse et al., 2010).

In addition to dysuria, frequency, and suprapubic pain there may be malaise, fever, night sweats, nocturia, and weight loss. In some patients there is back, flank, or abdominal pain, and occasionally macroscopic haematuria. Renal colic occurs in up to 10% of patients (Pasternack and Rubin, 1993). Only about one third of patients have an abnormal chest X-ray (Simon et al., 1977).

When renal tuberculosis is advanced and bilateral, a reduction in GFR due to generalized destruction of the parenchyma is likely and in some patients this progresses to end-stage renal failure. A more common cause for loss of GFR is ureteric scarring with distortion and obstruction, and fibrosis and contraction of the bladder—'thimble bladder'.

Tuberculous interstitial nephritis

In recent years, it has become clear that there is another more insidious form of renal tuberculosis (Morgan and Eastwood, 1990). In 1981, three patients were described (two from the Indian sub-continent and one from West Africa) with advanced renal failure in whom imaging revealed equal-sized smooth kidneys without evidence of calcification or gross anatomical distortion (Mallinson et al., 1981). Renal histology revealed interstitial infiltrates with chronic inflammatory cells and granulomas in all three patients, caseation in two, and acid-fast bacilli in two. In two patients there was radiological evidence of pulmonary tuberculosis and one patient had tuberculous peritonitis. This report emphasizes that there can be tuberculous involvement of the kidneys, sufficient to cause renal failure, in the absence of either the typical renal destruction with calcification and fibrosis, or urinary tract obstruction. Indeed, in these three cases, tubercle bacilli were neither seen in the urine nor grown from it. In a review of 3500 renal biopsies carried out in Paris over a 14-year period (Mignon et al., 1984), interstitial granulomas were found in 24. Three of these patients had tuberculosis and in one acid-fast bacilli were found in the kidney.

Benn and colleagues (1988) reported a Ugandan Asian woman (urea, 13.3 mmol/L; creatinine, 260 mmol/L; creatinine clearance, 17 mL/min) with equal-sized smooth kidneys on intravenous urography (IVU) in whom renal biopsy showed interstitial fibrosis with epithelioid and giant cell granulomas, one showing caseation. Acid-fast bacilli were not seen in, nor was *M. tuberculosis* grown from, biopsy material or urine. Her Mantoux test was strongly positive and antituberculous therapy for 12 months led to improvement in GFR (creatinine, 223 μmol/L; creatinine clearance, 39 mL/min) that was maintained for many years (Fig. 196.2). Tuberculosis had not been considered before the biopsy because, unlike some other reported cases (Mallinson et al., 1981), there was no evidence of tuberculosis elsewhere and five of the six mid-stream samples of urine were free of leucocytes. More recently, in a series of 25 cases of tuberculous interstitial nephritis from a single centre it has been shown that treatment of the tuberculosis can often lead to a sustainable increase of GFR although not often in those approaching end-stage renal disease (Chapagain et al., 2011). As in earlier studies, the patients were mostly immigrants from developing countries; all 25 were of Indo-Asian or African origin.

Box 196.1 Causes of a 'sterile' pyuria

- Tuberculosis of the urinary tract
- *Chlamydia trachomatis, Mycoplasma*, or *Ureaplasma* infection
- Chemically induced cystitis
- Renal calculi, prostatitis
- Coliform (or other pathogen) urinary tract infection but antibiotic inhibiting growth
- Failure to realize that low numbers of organisms can indicate infection
- White blood cells from outside urinary tract, for example, from foreskin or vulva
- Renal parenchymal cause—acute tubulointerstitial nephritis, glomerular disease.

Tuberculosis and glomerular disease

Glomerulonephritis complicating tuberculosis is rare (Sun et al., 2011) although there are a number of case reports including IgA nephropathy (Sun et al., 2011), dense deposit disease associated with tuberculosis (Hariprasad et al., 1979), and miliary tuberculosis with focal proliferative glomerulonephritis (Shribman et al., 1983). In neither case were granulomas seen. Interestingly, similar renal histology has been documented in lepromatous leprosy (Iveson et al., 1975).

Tuberculosis is an important cause of renal amyloidosis in India (and probably other developing countries too) and in one series caused a reduced GFR in 32 of the 42 cases described (Dixit et al., 2009). These authors pointed out that amyloidosis can progress despite adequate therapy for the tuberculosis and, contrary to commonly held belief, may commence early in the course of the disease. Renal amyloidosis should be considered in patients with tuberculosis who present with lower limb oedema, proteinuria, and echogenic kidneys on ultrasonography. The condition is rare in children but two cases associated with tuberculosis have been described (Krishnamurthy et al., 2009). Both children presented with nephrotic syndrome which resolved on successful treatment of the tuberculosis.

Tuberculosis in patients with chronic renal failure

It has been suggested that tuberculosis is more common in patients with renal failure than in the general population. In a study in west London, where there were significant numbers of refugees and asylum seekers from countries where tuberculosis is endemic, three

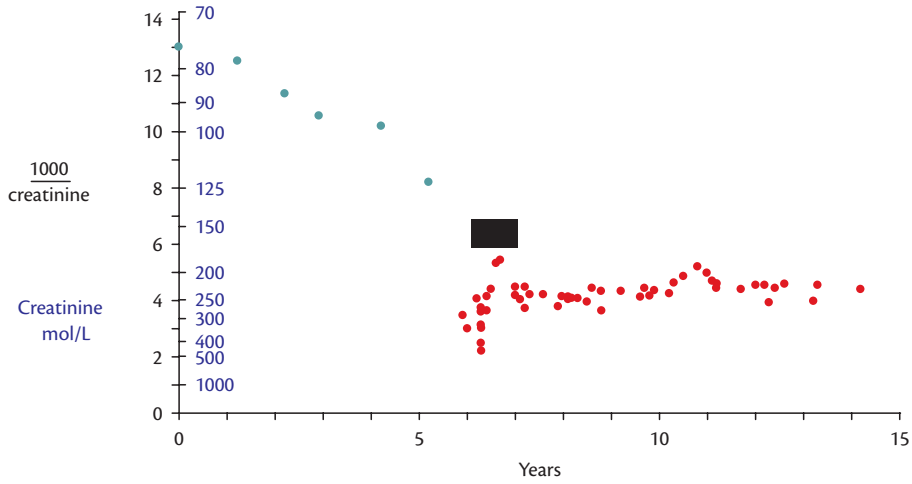

Fig. 196.2 Graph of reciprocal creatinine plot against time illustrating arrest of decline in renal function after treatment of renal tuberculosis. Bar indicates treatment with antituberculous drugs and prednisolone for 6 months.

factors were considered to be of importance (Moore et al., 2002)—being born overseas, the immunosuppressive effect of uraemia and the coexistence of diabetes mellitus and tuberculosis in patients with renal failure.

There is evidence for a state of relative immunological anergy in uraemia—as indicated by skin testing—but the incidence of tuberculin anergy is difficult to assess unless data on tuberculin reactivity before the onset of renal failure is available (Woeltje et al., 1998). On the other hand, use of common recall skin test antigens such as tetanus, *Candida*, and mumps revealed anergy in 32% of dialysis patients in one study (Woeltje et al., 1998) and in 40% in another (Smirnoff et al., 1998). A further study showed that 69% of uraemic patients commencing haemodialysis were anergic but that reactivity to common recall antigens was partly restored by haemodialysis, affecting 50% and 24% of patients on dialysis for 1–8 and 9–69 months respectively (Kaufmann et al., 1994). After 6 years the incidence of anergy rose again (to 46%). Other risk factors in the development of tuberculosis in patients with end-stage renal disease are diabetes, which accounts for about 20% of patients starting dialysis in the United Kingdom, and vitamin D deficiency, low circulating levels of 25-OH vitamin D being a common finding in patients with renal failure (Eastwood et al., 1979).

End-stage renal disease

Tuberculosis is an important cause of progressive renal failure (Benn et al., 1988). In 1991, the European Dialysis and Transplant Association (EDTA) registry reported that 195 (0.65%) of 30,064 new patients (from 35 European countries) assigned a renal diagnosis had renal failure due to tuberculosis, an incidence similar to that of earlier years (Eastwood et al., 1994). A report from Portugal showed that there may be local areas of high incidence (Neves et al., 1993). Over a 10-year period in the Algarve, tuberculosis was the cause of renal failure in 12 of 345 patients (3.5%) starting haemodialysis. In some instances, the patients presented terminally without having had any symptoms of tuberculosis. From published data on primary renal diagnosis, it is clear that tuberculosis is more common in Europe as a primary renal diagnosis (2247 cases (0.7%)) than in either the United States (0.004%) or Australasia (0.16%) (Maisonneuve et al., 2000).

The incidence of urinary tract tuberculosis as a cause of end-stage renal disease is probably being underestimated as, although many individuals with classical urinary tract tuberculosis are identified, the interstitial form is easily overlooked. Hence it is important that the diagnosis is considered in all patients with equal-sized smooth kidneys without a clear-cut renal diagnosis, especially in high-risk groups (Morgan et al., 1990; Chapagain et al., 2011). In such patients renal biopsy should always be considered.

Dialysis patients

Haemodialysis

Tuberculosis is a problem in haemodialysis patients, in whom it often presents in an insidious manner with anorexia, low-grade fever, and weight loss. In some reports, the majority of cases have been extrapulmonary or, occasionally, miliary (Sasaki et al., 1979; Hussein et al., 1990). Tuberculosis appears to be much more common among haemodialysis patients than in the general population (Smith, 1982) and the type of presentation suggests that dialysis is associated with re-activation of quiescent disease. Risk factors for tuberculosis include age (> 70 years old), low body-mass index, low serum albumin, anaemia, diabetes, tuberculin reactors, smoking, illicit drug use, healed tuberculous lesions on chest radiography, and duration of haemodialysis exceeding 1 year (Klote et al., 2006; Christopoulos et al., 2009b).

Among predominantly Caucasian dialysis populations ethnic minorities may be over-represented (Pazianas et al., 1991; Roderick et al., 1994), and they may have a higher incidence of tuberculosis (Kwan et al., 1991). Moore et al. (2002) described 11 cases, all born overseas, among dialysis patients at the Hammersmith Hospital, London. The incidence equates to an annual rate of 1187 per 100,000. In England and Wales in 1998, the overall rate was 12 per 100,000; among black Africans and individuals from the Indian subcontinent incidence rates were at the most 210 and 132 cases per 100,000 of the population. A study from Istanbul was more reassuring (Kazancioglu et al., 2010). Of 925 patients referred from other renal centres just 31 were found to have tuberculosis, a proportion that the authors felt represented improvement compared with previous years.

Peritoneal dialysis

There are fewer reports of tuberculosis among patients undergoing continuous ambulatory peritoneal dialysis (CAPD) (Cheng et al., 1989; Ahijado et al., 1991; Tan et al., 1991; Ong et al., 1992; Quantrill et al., 2001). All were patients on CAPD rather than the automated form (APD), and in six cases the organism was grown, mostly from the peritoneal fluid itself. The disease presented soon after starting dialysis and was indistinguishable clinically from bacterial peritonitis. A study of CAPD patients in 12 renal centres in Turkey revealed 10 cases of tuberculous peritonitis (Karayaylali et al., 2003). The authors concluded that tuberculous peritonitis is very rare in CAPD patients.

Transplant patients

Tuberculosis should always be considered when a renal transplant patient develops fever, especially when the patient is from a high-risk group, such as immigrants from areas with a high incidence of tuberculosis. Until recently tuberculosis has received less attention than opportunist infections such as *Pneumocystis jirovecii* (formerly *carinii*), Epstein–Barr virus, and cytomegalovirus. Indeed, when the literature was reviewed in 1983, when renal transplantation had been a part of nephrological practice for 30 years, only 42 cases of tuberculosis in patients with renal transplants were found (Lichtenstein and MacGregor, 1983). Subsequently, in Saudi Arabia, 14 cases were found among 403 renal transplant patients and the annual incidence of tuberculosis in these patients was about 50 times that of the general population (Qunibi et al., 1990). A particular finding in these and other Saudi Arabian patients (totalling 130 patients in all) was a high proportion of miliary disease (64% in the series of 14 patients, and 38% of the total of 130). Tuberculin test status did not appear to influence the risk of developing tuberculosis. The risk of developing tuberculosis post transplant is related to the degree of immunosuppression and the risk appear to be greater in those treated with the more potent immunosuppressive drugs mycophenolate mofetil and tacrolimus (Atasever et al., 2005).

The use of preventive therapy in renal transplant patients at risk of developing tuberculosis has been a controversial topic and until recently there has been no consensus on its use. In a meta-analysis of 11 clinical trials, nine showed risk reduction (Currie et al., 2010). On the basis of this meta-analysis it was recommended that preventive therapy should be used in all renal transplant patients in endemic regions and in those with risk factors in non-endemic regions but it was noted that the evidence is not robust. There have been concerns that the use of prophylactic isoniazid in transplant patients might increase the plasma ciclosporin level and induce ciclosporin nephrotoxicity. A recent detailed study, however, on seven renal transplant recipients with slow isoniazid acetylation status showed that the pharmacokinetics of ciclosporin were unaffected by isoniazid and it was concluded that concomitant administration of these drugs is safe (Sud et al., 2000). As yet, there are insufficient data to draw any firm conclusions as to the effect of isoniazid on the metabolism of tacrolimus or sirolimus. The British Thoracic Society guidelines (2010) recommend a 6-month course of isoniazid 300 mg daily plus pyridoxine 10–25 mg daily or, alternatively, a 3-month course of isoniazid, rifampicin, and pyridoxine or a 4–6-month course of rifampicin alone. Preventive therapy should also be given to tuberculin-negative patients who receive a kidney from a tuberculin-positive donor.

Tuberculosis of the genital tract

In the male, genital tuberculosis is acquired by seeding from infected urine or via the bloodstream. The commonest manifestation is epididymo-orchitis; less common is tuberculous prostatitis. Tuberculosis of the urethra and penis are much less common. The urinary tract should be fully investigated in any patient found to have genital tuberculosis; a study of 34 patients with tuberculous epididymo-orchitis showed that 64% had evidence of urinary tract involvement (Gómez Garcia et al., 2010).

Tuberculosis of the female genital tract is accompanied by urinary tract tuberculosis in < 5% of cases—far less commonly than in the male. Presumably, this is because the genital and urinary tracts in the female are separate so avoiding the possibility of direct infection of the genital tract from the urine. Thus tuberculosis of the female genital tract is probably almost always the result of haematogenous spread (Pasternack and Rubin, 1993).

Hypercalcaemia and tuberculosis

There have been reports of hypercalcaemia in patients on chronic haemodialysis with either disseminated or genitourinary tuberculosis (Felsenfeld et al., 1986; Peces and Alvarez, 1987; Peces et al., 1998). In one case, hypercalcaemia was not observed until the patient had been on dialysis for 8 months and its onset coincided with the development of widely disseminated tuberculosis presenting with persistent fever (Felsenfeld et al., 1986).

Hypercalcaemia was observed in all of six patients with tuberculosis and end-stage renal failure (Yonemura et al., 2004). Serum concentrations of calcitriol ($1,25\text{-}(OH)_2D_3$) were higher, and those of parathyroid hormone were lower, than in 110 patients with end-stage renal failure but not tuberculosis, suggesting enhanced extrarenal synthesis of calcitriol. Following antituberculous therapy the ratios of calcitriol and parathyroid hormone were similar to those in the non-tuberculosis group with renal failure.

Tuberculosis and HIV

The kidney is often involved in the disseminated tuberculosis characteristic of those infected with HIV but only a minority of patients have clinical features such as sterile pyuria and haematuria (Marques et al., 1996). In south-east England between 1984 and 1992, *M. tuberculosis* was isolated from the genitourinary system of 7 of 167 HIV-positive tuberculosis patients (Yates et al., 1993), but the low incidence may indicate a failure to culture relevant specimens from such patients in the absence of specific clinical symptoms. In a study in India, 17 of 35 patients dying of AIDS were found to have tuberculous lesions in their kidneys, with this disease being more common than fungal infections (five cases) and cytomegalovirus (two cases) (Lanjewar et al., 1999). The isolation of environmental mycobacteria from urine of HIV-positive patients is described in Chapter 197.

Imaging

Intravenous urography (IVU) is the most useful initial imaging for detecting urinary tract tuberculosis because of its ability to detect calcification, demonstrate abnormal anatomy, and to show the commonly occurring multiple lesions (Figs 196.3–196.8).

Renal tuberculosis may be unilateral or bilateral. Calcification is seen in about 30% of cases (Roylance et al., 1970), and it may have a

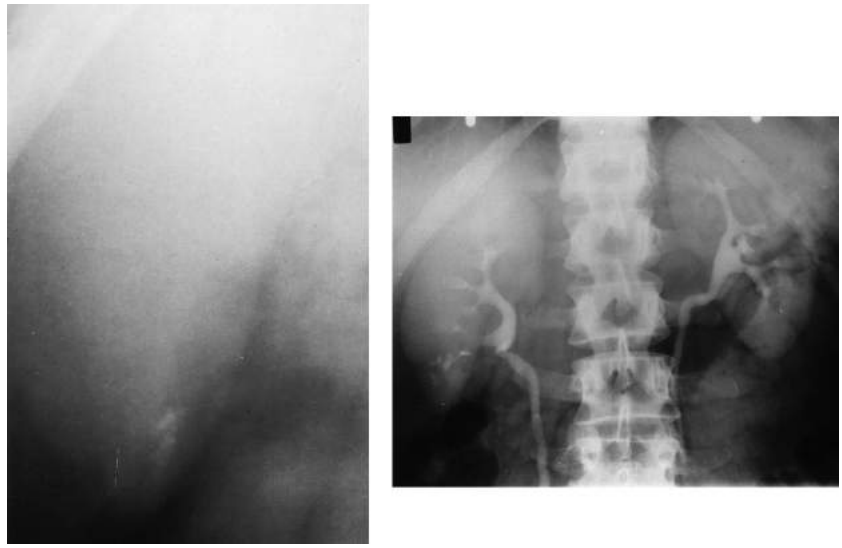

Fig. 196.3 Early focal renal tuberculosis. Plain film shows calcification in the lower pole of the right kidney. The 5-minute IVU film shows the abnormal lower pole calyx with loss of adjacent parenchyma. There was sterile pyuria and *Mycobacterium tuberculosis* was cultured from the urine.

variety of patterns—punctate, speckled, or hazy. In advanced tuberculosis the whole pelvicalyceal system and ureter may be outlined by calcification—the so-called tuberculous auto-nephrectomy.

Early tuberculosis is seen as irregularity of the papillary margins with reduced density of contrast medium in the affected areas. Cavities, either smooth or irregular, then develop and communicate with the pelvicalyceal system. As destruction progresses there is associated parenchymal loss. Fibrosis leads to strictures. When these affect the calyceal infundibula the calyces fail to fill on urography and the infundibulum shows a typical 'pinched-off' appearance. Fibrosis at the pelviureteric junction causes obstruction at this level. Local granuloma formation or dilated obstructed calyces that do not fill with contrast medium may produce a mass effect. Extension of infection into the perinephric space may lead to abscess formation. Fistulae may develop, particularly to the skin and gut.

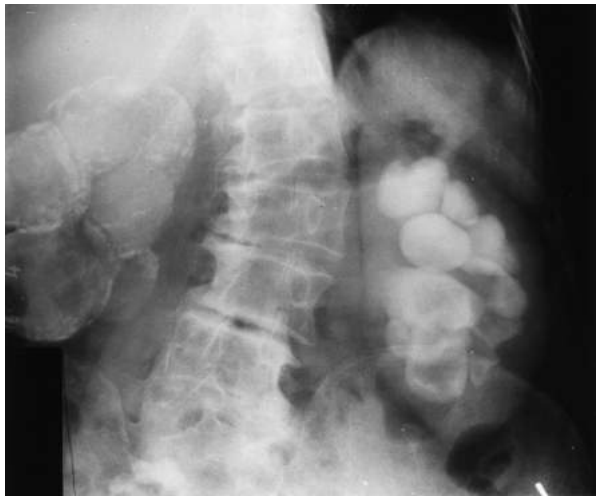

Fig. 196.4 Late bilateral renal tuberculosis. IVU film shows bilateral calyceal dilatation, calcified on the right.

Ureteric and bladder tuberculosis are secondary to renal tuberculosis. The earliest ureteric change is ulceration but this is rarely demonstrated radiologically. Strictures develop and there may be filling defects on IVU if there is florid granuloma formation. As fibrosis progresses the ureter shortens and becomes

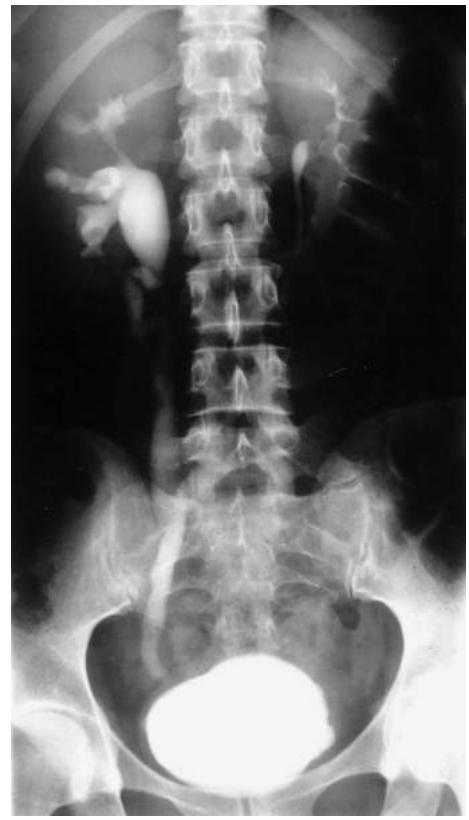

Fig. 196.5 Early changes of renal tuberculosis on 20-minute IVU film. There are cavities in the parenchyma adjacent to the right upper and interpolar calyces; there is dilatation of the right ureter. The left kidney is normal.

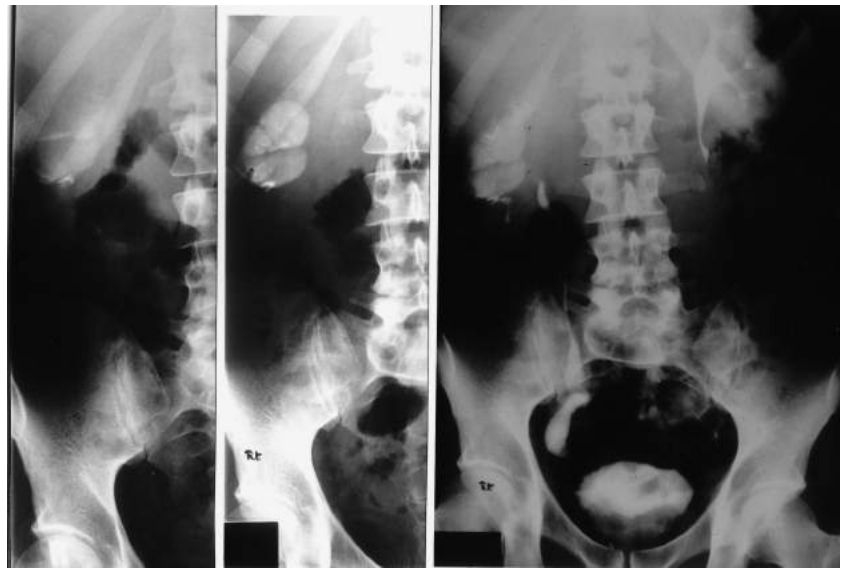

Fig. 196.6 Left-hand panel shows calcification in the right hypochondrium. Middle panel shows more pronounced calcification in the same area 9 years later. The 20-minute IVU film (right-hand panel) shows calyceal distortion and stricture, these appearances being typical of tuberculosis. The multifocal strictures and dilated segments of the ureter are typical late features of tuberculosis; there is also irregularity of the bladder wall. The left kidney is normal.

thick-walled. Sometimes incompetence at the vesicoureteric junction leads to reflux. The bladder wall tends to thicken and granulomas may cause filling defects. With generalized involvement, bladder capacity is reduced. Calcification in the ureters and bladder only occurs with advanced disease. Calcification may also occur in the seminal vesicles, vas, and prostate if these are involved.

Ultrasonography shows many of the changes of renal tuberculosis and is a useful adjunct to diagnosis (Vijayaraghavan et al., 2004; Rui et al., 2008), although urography, even in advanced disease, is also required (Premkumar et al., 1987). Ultrasonography and magnetic resonance imaging are useful alternatives to IVU in children, in whom reduction of exposure to radiation is an important consideration (Mapukata et al., 2007).

Computed tomography is useful for demonstrating the many changes in advanced disease: calcification, pelvicalyceal dilatation, scars, strictures, and extrarenal spread (Goldman et al., 1985; Premkumar et al., 1987). Its sensitivity in early disease has not been assessed.

Follow-up studies of patients on antituberculous drugs show that ureteric strictures can develop during treatment. They may occur at sites apparently normal on the IVU obtained at presentation, presumably because mucosal ulceration at the affected site was not visualized.

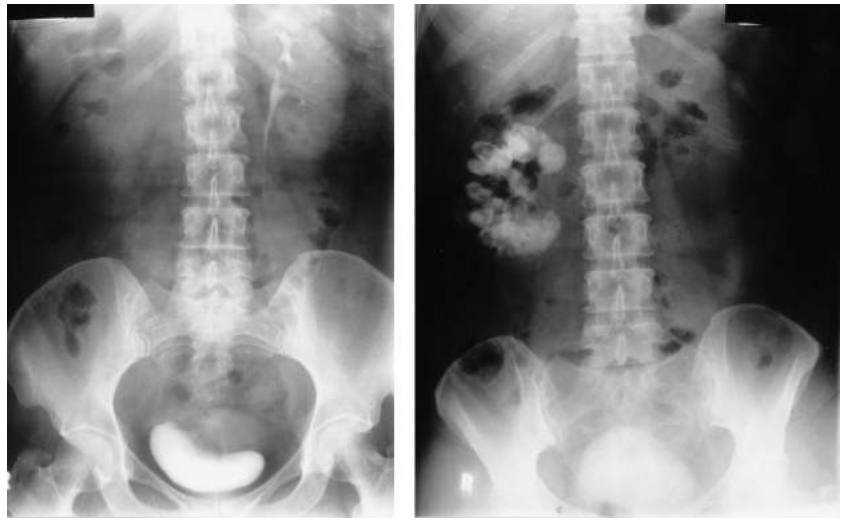

Fig. 196.7 Left-hand panel shows 30-minute IVU film—normal left kidney and ureter with lack of excretion on the right. Right-hand panel shows 1-hour film. Contrast is no longer seen in the collecting system on the left side but there is opacification of a grossly distorted kidney on the right side. This appearance is typical of the eventual tuberculous 'autonephrectomy' that sometimes occurs. The lack of calcification is unusual.

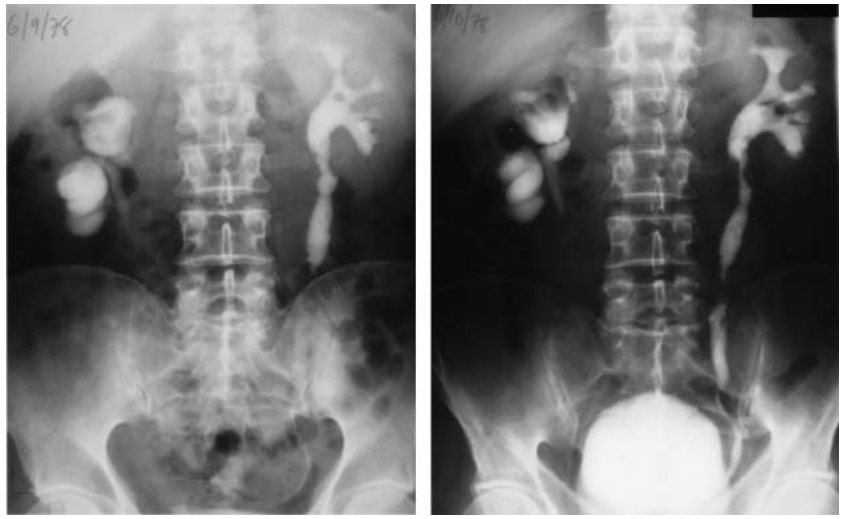

Fig. 196.8 Two 10-minute IVU films taken 1 month apart. Note the mural abnormalities in the ureter (left-hand panel) that have progressed to frank strictures 1 month later. The right kidney shows global calyceal dilatation.

Microbiology

The diagnosis is made by bacteriological examination of urine or tissue biopsies. Ideally, early morning mid-stream urine specimens collected on 3 successive days are examined. The most suitable containers are sterile 28 mL Universal Containers. Specimens should be delivered to the laboratory as quickly as possible to prevent replication of bacterial and fungal contaminants. When delays are unavoidable, samples should be refrigerated but not frozen.

Urine samples are centrifuged and deposits examined microscopically after staining by the Ziehl–Neelsen or similar acid-fast techniques. As contamination by EM is common, genitourinary tuberculosis should never be diagnosed on the basis of microscopic evidence alone. Tissue biopsies reveal the characteristic histological appearances and acid-fast bacilli. Failure to detect acid-fast bacilli on microscopic examination does not rule out their presence in the specimen. Tissue must contain 10^4–10^5 acid-fast bacilli per gram for them to be detected microscopically.

Egg-based media, such as Löwenstein–Jensen medium have been the mainstay of mycobacterial culture but colonies of *M. tuberculosis* take 2–8 weeks to appear. More rapid culture systems have therefore been introduced, which allow mycobacterial growth to be detected within 2–10 days.

Nucleic acid amplification techniques have been extensively investigated for their ability to detect mycobacteria rapidly in clinical specimens. The use of PCR for the diagnosis of genitourinary tuberculosis has been less thoroughly investigated but available data show that the techniques are sensitive and specific (Hemal et al., 2000) but not sensitive enough to be used as the sole diagnostic method (Yazdini et al., 2008). Some urine specimens contain substances that inhibit the PCR (van Vollenhoven et al., 1996; Sechi et al., 1997). On the other hand, PCR on renal biopsy specimens has been shown to be a rapid, sensitive, and specific diagnostic test for early-stage renal tuberculosis (Sun et al., 2010). PCR has also been used to detect mycobacterial DNA in urine in cases of disseminated tuberculosis in HIV-positive people (Aceti et al., 1999).

In central reference laboratories mycobacteria are usually identified by culture and biochemical tests, or by more rapid nucleic acid-based methods. Drug susceptibility testing is traditionally based on demonstrating growth inhibition on drug-containing solid media but results will not be available for several weeks. The automated systems mentioned above provide a more rapid means for achieving such information. Resistance to isoniazid and rifampicin can be established using very accurate rapid molecular techniques (Ling et al., 2008).

Traditional laboratory procedures for isolation, identification, and drug susceptibility testing of mycobacteria are described in detail by Collins et al. (1997) and the application of rapid molecular technology is reviewed by Drobniewski et al. (2013).

Immunology

The tuberculin skin test is the time-honoured method of diagnosing past infection by members of the *M. tuberculosis* complex but it does not differentiate latent from active tuberculosis, and past BCG vaccination can result in a positive reaction. In addition, the test may be negative in immunosuppressed patients, including those with chronic renal failure, or on dialysis, or taking post-transplant immunosuppressive therapy. A more recent test system is based on the release of gamma-interferon from peripheral blood lymphocytes when incubated with mycobacterial antigens specific for virulent members of the *M. tuberculosis* complex but absent from BCG. The lack of a highly specific means for differentiating latent from active tuberculosis renders comparisons between tuberculin testing and interferon-gamma release assays (IGRA) difficult. Limited experience indicates that the latter correlate more closely with risk factors than the former for tuberculosis in dialysis patients (Hoffmann et al., 2010; Lee et al., 2010). While some authors suggest that IGRA should replace tuberculin skin testing in dialysis patients (Segall and Covic, 2010), others believe

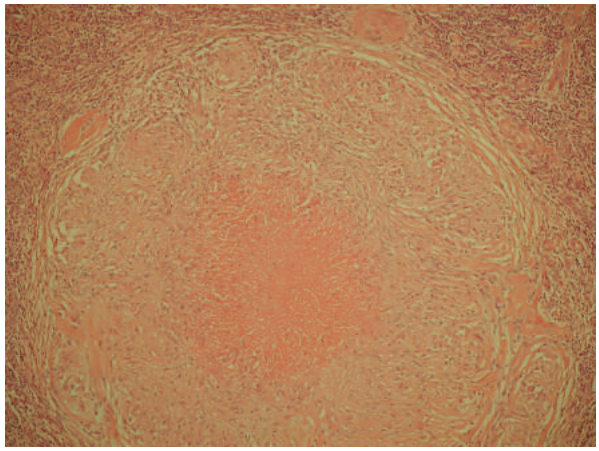

Fig. 196.9 Caseating epithelioid granuloma, the histological hallmark of classical tuberculosis.

that it should complement, but not replace, the latter (Palomar et al., 2011).

There are several commercial serological tests for active tuberculosis based on antibody detection but the WHO (2011) strongly advises against their use as they yield inaccurate results.

Histopathology

The morphology of the lesions depends on the type of infection, the virulence of the organism and the immune status of the patient. The characteristic microscopic lesion of mycobacterial infection is the caseating epithelioid granuloma (Fig. 196.9), but caseation may not always be apparent, notably in overwhelming or miliary infections, disease due to environmental mycobacteria, BCG-related lesions, and in leprosy. Although acid-fast bacilli may often be demonstrated in early active disease and in lesions in the immunosuppressed (Ridley and Ridley, 1987) (Fig. 196.10), they may be difficult or impossible to identify in immunocompetent or treated patients, and in old lesions. Fluorescent methods of identification are more sensitive. PCR on formalin-fixed and paraffin-processed tissue sections may be misleading.

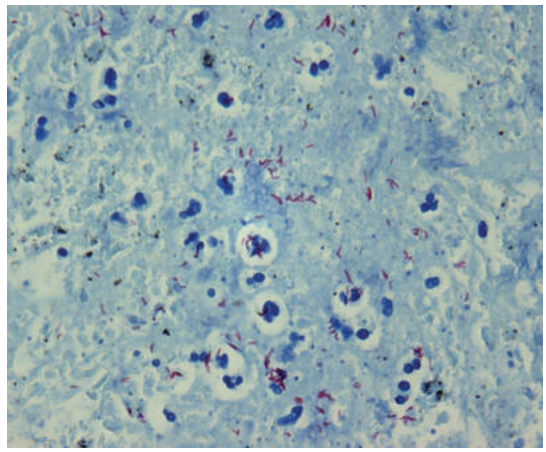

Fig. 196.10 Large numbers of acid- and alcohol-fast bacilli in a caseating granuloma in an immunosuppressed patient with overwhelming infection. Ziehl–Nielsen stain.

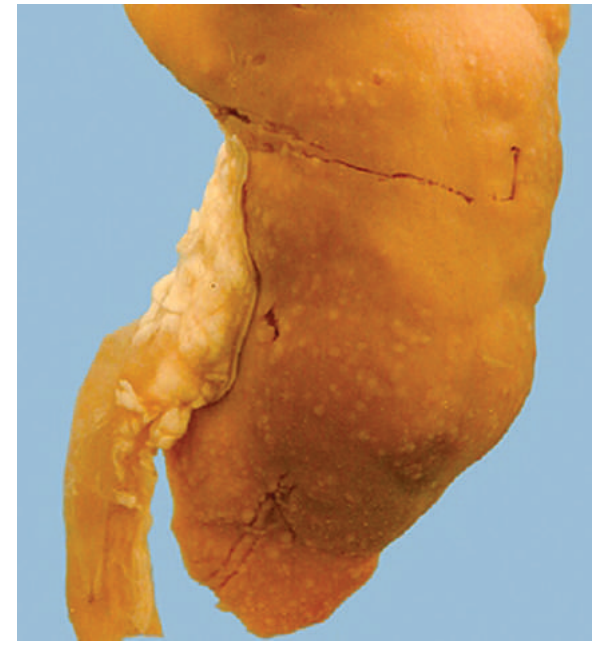

Fig. 196.11 Miliary tuberculosis involving the renal cortex. Typical tubercles are seen on the cortical surface; they were also present within the renal parenchyma.

Healing produces scarring and frequently calcification. The differential diagnosis of necrotizing granulomas in the renal tract includes fungal infections and Wegener's granulomatosis. Non-caseating granulomas may be seen in sarcoidosis, leprosy and brucellosis. 'Foreign body type' granulomas which are occasionally seen in response to amyloid, ruptured tubules, myeloma protein and therapeutic embolization.

Disseminated infection

The kidney is frequently involved in miliary tuberculosis (Fig. 196.11). The lesions measure up to 3 mm in size and are usually pale or white. Histologically, they consist of epithelioid granulomas, with or without caseation, and often contain Langhans-type giant cells. Organisms can usually be demonstrated within these lesions, but are often difficult to find. Renal function usually remains normal.

In immunosuppressed patients the granulomas may be less well formed and organisms more readily demonstrated. Caseous necrosis, which is the result of cell-mediated hypersensitivity and therefore dependent on an effective immune response, is less frequently seen. When immunosuppression is severe, and in cases where the infective organism is an environmental mycobacterium (Horsburgh, 1991), the lesions may be more diffuse and poorly formed and the response consists of histiocytic cells packed with organisms ('multi-bacillary histiocytosis'). Necrosis is not a feature.

In some patients there is evidence of renal failure without typical miliary involvement or localized genitourinary lesions. In these cases, biopsy has shown interstitial nephritis, usually, but not in all cases, with granulomas (Fig. 196.12) (Chapagain et al., 2011; Chaudhari et al., 2011; Eastwood et al., 2011). Proliferative

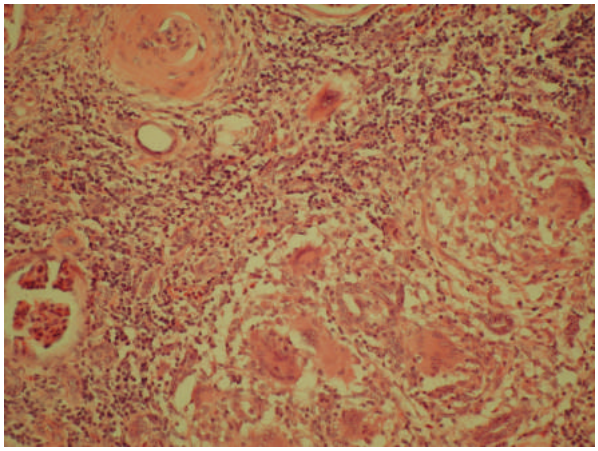

Fig. 196.12 Granulomatous interstitial nephritis; note that the glomerulus is normal.

glomerulonephritis due to immune-complex disease has also been reported (Shribman et al., 1983).

Localized infection

The kidney is usually infected by haematogenous spread from the lung but it is unusual for there to be evidence of active pulmonary disease when renal involvement becomes manifest. There may be clinical or radiological evidence of past infection indicating that the renal component arises as a result of reactivation rather than as a new infection (Christensen, 1974; Narayana, 1982). Clinically, renal tuberculosis presents as unilateral involvement but studies undertaken in the pre-chemotherapeutic era indicate that the disease is frequently bilateral at autopsy (Kretschmer 1930; Greenberger et al., 1935).

If a tuberculous lesion in the lung gains access to the vascular system by erosion of the wall of a vessel, usually a vein, emboli containing organisms may be disseminated throughout the body. However, they proliferate in a small number of sites including kidney, epididymis, fallopian tube, bone marrow, brain, particularly the hindbrain, and the adrenal gland. The infection may cause vascular insufficiency by damaging blood vessels and papillary necrosis may ensue (Fig. 196.13). Spread to the renal pelvis produces tuberculous pyelonephritis and may even progress to a pyonephrosis-like lesion, also known as a 'cement' or 'putty' kidney (Fig. 196.14). Scarring develops within the renal pelvis with calcification in 24%. The clinical consequences of an extensive renal lesion include autonephrectomy. The destructive renal lesions occasionally spread outside the renal capsule and produce a mass lesion that can mimic a neoplasm (Njeh et al., 1993).

Lower urinary tract involvement

Ureteric involvement may also produce irregular ureteric strictures (Fig. 196.15), segmental dilatation, obstruction and/or reflux. Scarring around the ureteric orifice with reflux may produce a 'golf-hole' appearance (Christensen, 1974; Ramanathan et al., 1998). Keratinizing squamous metaplasia (previously known as leucoplakia) may develop as a late complication of chronic inflammation and infection (Fig. 196.16) (Byrd et al., 1976). Keratinizing squamous metaplasia is a risk factor for the development of squamous carcinoma.

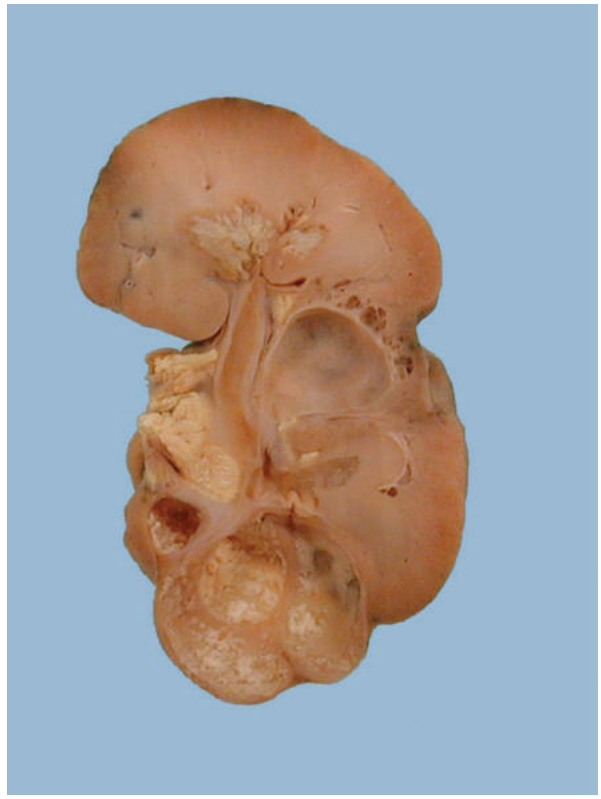

Fig. 196.13 Tuberculous involvement of the renal papillae with papillary necrosis. The ureter is also involved and shows mucosal irregularity and dilatation.

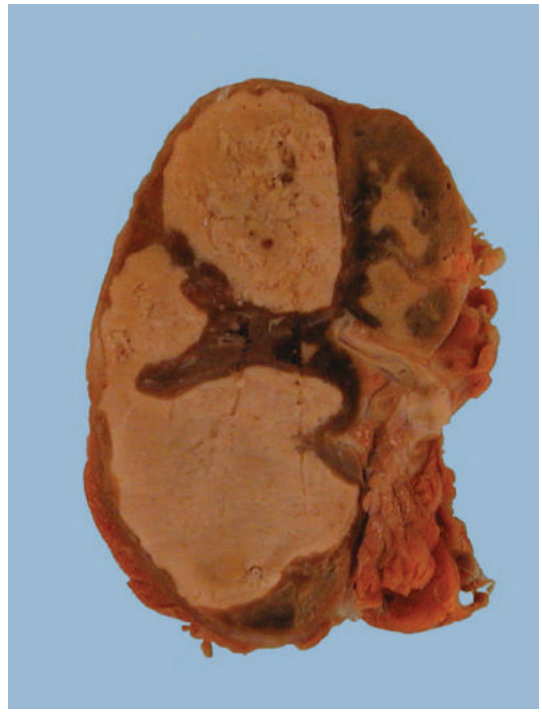

Fig. 196.14 Tuberculous 'pyonephrosis' with extensive caseous necrosis and renal parenchymal destruction. 'Cement' or 'putty' kidney.

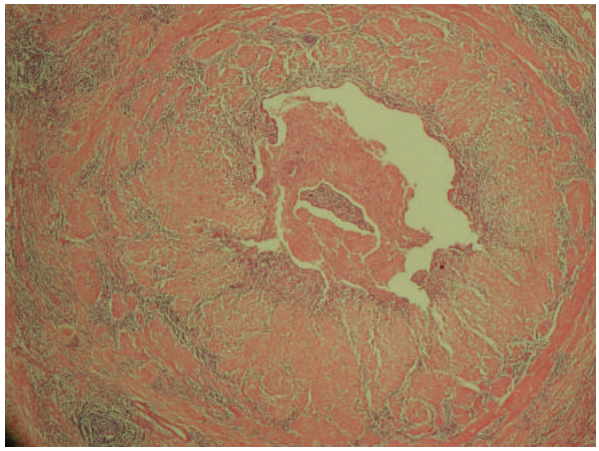

Fig. 196.15 Tuberculous stricture of the ureter with mucosal and mural inflammation and thickening.

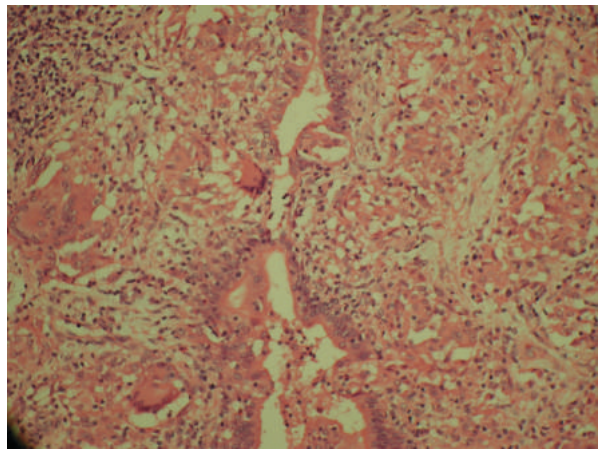

Fig. 196.17 BCG-induced granulomatous prostatitis in a cysto-prostatectomy specimen. Patient had been treated with intravesical BCG for transitional carcinoma *in situ* of the bladder.

BCG-induced urinary tract infection

The use of intravesical BCG has improved the prognosis of both urothelial transitional carcinoma *in situ* and high-risk superficial bladder cancer (grade 3 pTis and grade 3 pTa and pTl) (Sobin et al., 2009). This treatment usually causes only a self-limiting superficial cystitis, but sometimes the inflammatory reaction is more severe. There are reports of both disseminated infection with BCG and reflux of the organisms up the ureter causing ureteric obstruction, the latter occurring in 0.3% patients (Lamm 1992, 2000; Lamm et al., 2010). Renal involvement was recorded in 0.1% of these patients and is presumed to have arisen from ascending infection rather than haematogenous spread. The infection frequently involves the prostate. Histologically, the lesions caused by BCG are indistinguishable from those seen in classical tuberculosis and caseation may be present, more frequently in the prostate (Fig. 196.17) than in the bladder (Fig. 196.18).

Treatment

The WHO currently recommends that all newly-diagnosed patients with tuberculosis, irrespective of the site or severity of disease, should be treated with the four first-line drugs (group 1 in Table 196.3), rifampicin, isoniazid, pyrazinamide, and ethambutol, for 2 months, followed by a continuation phase of rifampicin and isoniazid for a further 4 months (WHO, 2009).

In cases of MDR-TB, alternative drugs in groups 2–5 listed in Table 196.3 are used. Treatment is, ideally, guided by rapid drug susceptibility testing or, when this is not available, by local guidelines based on prevalent patterns of drug resistance. Single drugs must never be added blindly to failing treatment regimens. These drugs are generally more toxic, more expensive, and less active than the first-line drugs and treatment is often prolonged and costly. For details of the management of MDR-TB see WHO (2008).

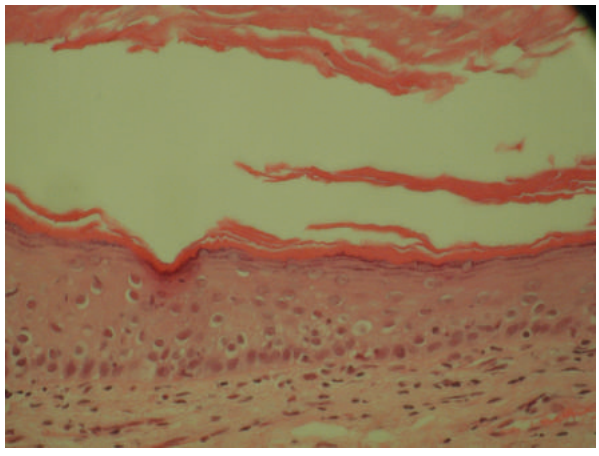

Fig. 196.16 Keratinizing squamous metaplasia of the bladder. There is no epithelial dysplasia but such cases carry an increased risk of developing squamous cell carcinoma.

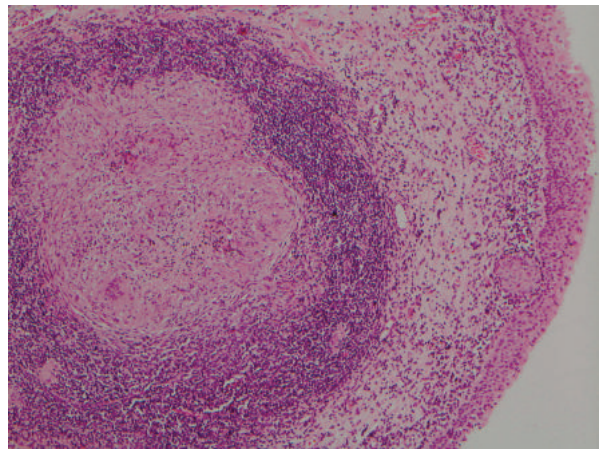

Fig. 196.18 Bladder mucosal biopsy in patient being treated for urothelial carcinoma *in situ* with intravesical BCG. A typical non-caseating epithelioid granuloma is present in the lamina propria. The overlying urothelium shows reactive changes but no carcinoma *in situ*.

Table 196.3 The five classes of antituberculous drugs (World Health Organization, 2009)

Group 1: first-line oral drugs	Rifampicin
	Isoniazid
	Ethambutol
	Pyrazinamide
Group 2: injectable drugs	Capreomycin
	Amikacin
	Streptomycin
	Kanamycin
Group 3: fluoroquinolones	Levofloxacin
	Ofloxacin
	Moxifloxacin
Group 4: oral bacteriostatic second-line drugs	*Para*-aminosalicylic acid
	Cycloserine
	Terizidone
	Ethionamide
	Prothionamide
Group 5: drugs with as yet unclear roles in the treatment of drug resistant tuberculosis	Clofazimine
	Linezolid
	Amoxicillin/clavulanate
	Thioacetazone
	Imipenem/cilastatin
	High-dose isoniazid
	Clarithromycin

Table 196.4 Adverse effects of the four first-line oral antituberculous drugs

Drug	Adverse effects
Isoniazid	*Uncommon*: hepatitis, cutaneous hypersensitivity reactions including erythema multiforme, peripheral neuropathy
	Rare: vertigo, convulsions, optic neuritis and atrophy, psychiatric disturbance, haemolytic anaemia, aplastic anaemia, dermal reactions including pellagra, purpura and lupoid syndrome, gynaecomastia, arthralgia
Rifampicin	*Uncommon*: hepatitis, flushing, itching with or without a rash, gastrointestinal upsets, flu-like syndrome, headache
	Rare: dyspnoea, hypotension with or without shock, Addinsonian crisis, haemolytic anaemia, acute kidney injury, thrombocytopenia with or without purpura, transient leucopenia or eosinophilia, menstrual disturbances, muscular weakness, pseudomembranous colitis
Pyrazinamide	*Common*: anorexia
	Uncommon: hepatitis, nausea and vomiting, urticaria, arthralgia
	Rare: sideroblastic anaemia, photosensitization, gout, dysuria, aggravation of peptic ulcer
Ethambutol	*Uncommon*: optic neuritis, arthralgia
	Rare: hepatitis, cutaneous hypersensitivity reactions including pruritis and urticaria, photosensitive lichenoid eruptions, paraesthesia of the extremities, interstitial nephritis

The WHO currently recommends that tuberculosis patients with renal failure should be treated for 6 months with daily isoniazid and rifampicin throughout and thrice-weekly ethambutol (15 mg/kg) and pyrazinamide (25 mg/kg) for the first 2 months. Streptomycin should be avoided but, if its use is essential, 15 mg/kg should be injected two to three times weekly, with regular monitoring of drug levels.

Acute kidney injury due to rifampicin hypersensitivity is an uncommon complication of therapy and is most likely to occur with intermittent rather than daily therapy (Muthukumar et al., 2002). Recovery of renal function occurs after withdrawal of the drug.

Ethambutol is eliminated principally by the kidney and reduced doses should be given according to GFR (Mitchison and Ellard, 1980; Girling, 1989). The major adverse effects of the first-line drugs are listed in Table 196.4.

Encephalopathy, normally a rare complication of isoniazid therapy, can occur in patients with renal failure, although its incidence is reduced by the prescription of pyridoxine, 25–50 mg/day. (Cheung et al., 1993).

Care should be taken with rifampicin in renal transplant patients as it increases the catabolism of many drugs (Finch et al., 2002; British Thoracic Society, 2010). Rifabutin is sometimes used as an alternative to rifampicin as it is less potent as an inducer of the microsomal P450 enzymes involved in the metabolism of many of these drugs (EBPG Expert Group on Renal Transplantation, 2002).

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CHAPTER 197

Mycobacterial infections: leprosy and environmental mycobacteria

John Eastwood, Cathy Corbishley, and John Grange

Leprosy

In 2009, worldwide notifications of leprosy amounted to 244,796 new cases, a significant fall compared with 514,718 in 2003 (World Health Organization (WHO), 2010). Elimination of leprosy as a public health problem, defined as a prevalence of registered cases of < 1 per 10,000 population, has been achieved in many countries where leprosy was once highly endemic, and most others are close to reaching this stage. The global distribution of leprosy in 2011 is shown in Fig. 197.1 (WHO, 2012).

Leprosy and renal disease

Direct involvement of the kidney by *Mycobacterium leprae* is unusual. Epithelioid granulomas compatible with lepromas do occur, but acid-fast bacilli are seen only very rarely (Ahsan et al., 1995). Despite the rarity of direct bacillary invasion, renal damage is a major cause of morbidity and mortality in patients with leprosy (Iveson et al., 1975; Ng et al., 1981; Date et al., 1985; Chopra et al., 1991; Ahsan et al., 1995). Between 11% and 38% of leprosy patients die of renal failure (Ridley, 1988, pp. 89–90) but the incidence of milder or resolving renal disease detectable on biopsy is higher (Date and Johny, 1975). There have also been reports of various forms of tubulointerstitial disease (Ahsan et al., 1995), and urinary concentrating and acidification defects (Chugh et al., 1983). In one study in Brazil in patients with paucibacillary and multi-bacillary leprosy, urinary acidification defects were found in 32% and 29% respectively and urinary concentrating defects in 83% and 85% (Oliveira et al., 2008).

The relative incidence of the various types of renal disease in leprosy varies greatly. In an autopsy study in Brazil of 199 patients with leprosy dying between 1970 and 1986, renal lesions were found in 144 (72%) (Nakayama et al., 2001). Renal amyloid was detected in 61 patients (42.7% of those with renal lesions), glomerulonephritis in 29 (20.2%), nephrosclerosis in 22 (15.3%), tubulointerstitial nephritis in 18 (12.5%), granulomas in two, and other lesions in 12.

The risk of glomerulonephritis in leprosy may be related to mycobacterial load as it seems to occur most frequently in patients with multi-bacillary (lepromatous and borderline lepromatous) leprosy, with immune complexes being seen in glomeruli (Date and Johny, 1975; Ng et al., 1981; Date et al., 1985; da Silva Júnior et al., 2006). Immunoglobulin (Ig)-G, IgM, and C3 have all been reported in the renal lesions although it is uncertain whether the antigen responsible for the immune complex formation and deposition is of mycobacterial origin (Date et al., 1977). Impairment of renal function is common during acute episodes of erythema nodosum leprosum (ENL) but, improves during periods of quiescence (Bajaj et al., 1981a; Kanwar et al., 1984). Opinions differ as to whether glomerulonephritis is more common in patients with ENL (Drutz and Gutman, 1973; Ng et al., 1981; Al-Mohaya et al., 1988).

Amyloidosis is also associated with multi-bacillary leprosy and its geographical incidence varies considerably. Leprosy-related renal amyloidosis appears to be relatively less frequent in the Indian subcontinent (Chugh et al., 1981; Nigam et al., 1986; Jayalakshmi et al., 1987) and Japan (Ozaki and Furuta, 1975), than elsewhere but the reason for this is unclear. In the Brazilian autopsy study referred to above (Nakayama et al., 2001), amyloidosis was more common in those with lepromatous leprosy (36%) than in those with tuberculoid or borderline disease (5%), and occurred most frequently in patients with recurrent ENL and trophic ulcers. In the same report, 95% of the patients with renal amyloid had proteinuria and 88% renal failure, with the latter being a common cause of death. Repeated flare-ups of ENL appear to be an important factor in the development of amyloidosis (McAdam et al., 1975).

It is important to evaluate renal function in all patients with leprosy in order to try to prevent progressive loss of renal function (da Silva Júnior et al., 2006). In a search for early markers of renal damage, Kirsztajn et al. (1993) studied 96 patients with leprosy who had normal serum creatinine levels and found haematuria in 22%, microalbuminuria in16%, and elevated levels of urinary β_2-microglobulin in 20%. In India, significant impairment of renal function was common in a group of 122 patients with lepromatous leprosy, notably in those with ENL (Bajaj et al., 1981b). Although many patients had diminished creatinine clearance and proteinuria, serum creatinine levels were significantly increased only in patients with active ENL.

Leprosy has been described in renal transplant patients (Ardalan et al., 2011). In one report of four patients (Roselino et al., 1993), two, who had the disease before the transplant, did not relapse but two presented with new disease (one lepromatous, one borderline) after the transplant. In another report, from the Indian

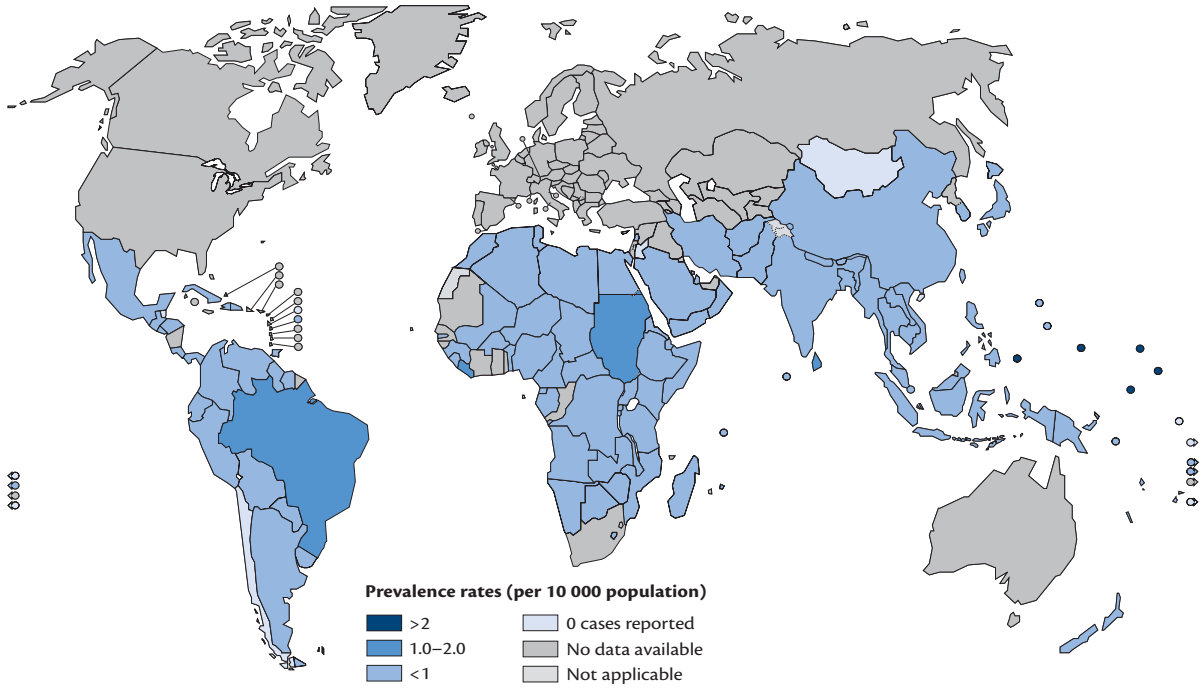

Fig. 197.1 Leprosy prevalence rates, January 2011.
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subcontinent (Date et al., 1998), three of nine renal transplant patients were known to have leprosy before transplantation. After transplant one had an exacerbation of previously unrecognized leprosy and five developed new disease 22 months to 12 years later. In most cases the immunosuppressive drugs seemed to have no adverse effect on treatment of the disease but in one patient who developed multi-bacillary leprosy 11 years after renal transplantation, extended multidrug therapy with the addition of prednisolone and thalidomide for treatment of multiple ENL reactions was required (Guditi et al., 2009).

Leprosy and genital lesions

While direct invasion of the kidney by *M. leprae* is rare, bacillary invasion of the testis is common in multi-bacillary leprosy. Patients with lepromatous or, less often, borderline lepromatous leprosy may present with painful swollen testes, sometimes associated with ENL reactions (Akhtar et al., 1980).

In addition to orchitis, chronic testicular involvement may lead to small soft testicles with impaired sensation, oligospermia, and azoospermia (Nigam et al., 1988). Hormonal changes, including reduction of the level of testosterone and elevation of luteinizing hormone, follicle stimulating hormone, and oestradiol levels (Saporta and Yuksel, 1994), may result in gynaecomastia and reduction of sexual function. Infertility is common. The epididymis may also be involved and in some cases where the patients have had relatively normal testes, azoospermia and infertility have been due to fibrous obstruction in the ducts of the epididymis (Ibrahiem et al., 1979).

Histological examination of the testis and epididymis reveals typical lepromatous lesions or a very variable and poorly defined pattern of vascular and obliterative changes (Kumar et al., 1982; Nigam et al., 1988).

Leprosy does not involve the female genital tract. In a study of the reproductive organs of women with the disease there was no evidence of either granulomas or acid-fast bacilli in endometrial biopsies or products of conception, and no acid-fast bacilli were found in menstrual blood. There was no evidence of any effect of leprosy on menarche, menstruation, fertility, or menopause (Sharma et al., 1981).

Treatment

Treatment is with standard multidrug regimens based on rifampicin, dapsone, and clofazimine (WHO, 2000). An alternative regimen, of comparable efficacy and tolerability, is based on rifampicin, ofloxacin, and minocycline (Villahermosa et al., 2004). Treatment has been made available by the WHO free of charge to all patients worldwide since 1995, and provides a simple yet highly effective cure for all types of the disease. Renal complications of the treatment are very rare and include acute kidney injury due to dapsone hypersensitivity (Alves-Rodrigues et al., 2005) and, as in tuberculosis, to rifampicin hypersensitivity (Gupta et al., 1992; Namisato and Ogawa, 2000).

Environmental mycobacteria

Urinary tract involvement

Disease of the genitourinary system due to environmental mycobacteria (EM) is exceedingly rare. Diagnosis poses serious problems in view of the frequency with which such bacteria are harmless contaminants of urine. Between 1980 and 1989, 572 EM cultured from urine in south-east England were submitted to the regional mycobacterium reference centre but, with five possible exceptions, all appeared to be contaminants (Grange and Yates, 1992). Brooker and Aufderheide (1980) proposed six criteria for the diagnosis of such disease:

- symptoms of chronic or recurrent genitourinary infection
- radiological or endoscopic evidence of genitourinary disease
- abnormalities on urine analysis
- failure to isolate other urinary tract pathogens
- repeated isolations of the same mycobacterial species
- histological demonstration of granulomas and, preferably, acid-fast bacilli.

The first four criteria should alert the clinician to the possibility of a mycobacterial aetiology, the fifth strongly suggests the diagnosis, but only the sixth is confirmatory. A retrospective application of these criteria failed to confirm the diagnosis in 19 supposed cases (Brooker and Aufderheide, 1980).

Very few confirmed cases of renal disease due to EM have been reported. Two patients with disease caused by *Mycobacterium intracellulare* (termed the 'Battey bacillus' in the older literature) were treated successfully by nephrectomy (Faber et al., 1965; Pergament et al., 1974), and one by nephro-ureterectomy (Newman, 1970). A further patient with pulmonary disease due to a slow-growing, non-chromogenic mycobacterium (a description compatible with *M. intracellulare*) developed a renal abscess due to an identical strain (Tsai et al., 1968). A case of renal disease due to *M. fortuitum* in an immunocompetent woman with urolithiasis presenting with fever and lumbar pain has been described (Serra et al., 2007). The infection responded to a 14-day course of ofloxacin (400 mg twice daily) and the patient became asymptomatic.

Cases have been described in immunocompromised patients but may well have been renal manifestations of disseminated disease. A few cases of *M. fortuitum* infection in patients receiving corticosteroid therapy have been reported (Serra et al., 2007), as has a case of *M. gordonae* infection in a renal transplant patient (Pinho et al., 2009); in the latter case the difficulty in distinguishing between true infection and colonization was discussed.

Four cases of epididymitis have been reported, one due to *M. xenopi* (Engbeck et al., 1967), one to *M. haemophilum* (Keller et al., 2008), and two to *M. kansasii* (Wood et al., 1956; Hepper et al., 1971). Both *M. xenopi* and *M. fortuitum* were isolated from a case of prostatitis with a granulomatous appearance compatible with mycobacterial disease (Lee et al., 1977). Infection by *M. avium* subspecies *intracellulare* presented as a testicular mass in a 62-year-old man immunocompromised by chemotherapy for diffuse B-cell lymphoma (Hartley, 2009).

A case of immune-complex-mediated crescentic glomerulonephritis in a patient with pulmonary disease due to *M. avium* has been reported (Wen and Chen, 2008). Renal function steadily improved on successful treatment of the underlying infection.

Complicating the treatment of end-stage renal disease

Dialysis patients

Haemodialysis

Small clusters and isolated cases of disseminated disease due to *M. chelonae* have occurred in patients on haemodialysis (Lowry et al., 1990). In some cases, the cause was contamination of the dialysis machine by *M. chelonae*. In one case reported from a hospital haemodialysis unit (Azadian et al., 1981), isolates from the patient and the resin used to soften the water were shown to have enzymatically identical profiles (Sparks and Ross, 1981).

Peritoneal dialysis

EM disease can be a complication of chronic peritoneal dialysis, the usual causes being *M. chelonae, M. abscessum, M. fortuitum*, and *M. kansasii* (Dunmire and Breyer, 1991; White et al., 1993). The reports emphasize the importance, in any case of continuous ambulatory peritoneal dialysis -related peritonitis with repeatedly negative 'routine' cultures, of culturing the fluid on media suitable for isolating mycobacteria. There is, however, no straightforward way of determining whether a mycobacterium isolated from peritoneal dialysis fluid is a pathogen or behaving as a saprophyte. A number of species otherwise rarely encountered as pathogens, including *M. gordonae* (London et al., 1988), *M. heckeshornense* (Chan et al., 2010), *M. gastri, M. porcinum, M. rhodesiae*, and *M. smegmatis*, have been isolated from peritoneal dialysis fluid and regarded as pathogens.

Standard management is to remove the catheter and treat with the appropriate drugs (White et al., 1993).

Transplant patients

Renal transplantation with the accompanying iatrogenic immunosuppression predisposes the patient to mycobacterial disease (Sinnott and Emmanuel, 1990). The incidence of such disease in these patients is higher than in the general population and in 25–40% of cases the cause is an EM. The development of clinical tuberculosis is usually the result of reactivation of dormant foci; the disease may be confined to the lung or involve many organs. Disease due to EM may also be localized to the lung or disseminated, but is often a cutaneous problem, typical organisms being *M. kansasii, M. haemophilum, M. marinum, M. chelonae*, and *M. fortuitum* (Kaur et al., 2011). The great majority of reports of *M. haemophilum* infection have been of cases of cutaneous involvement (Rajpara et al., 2010). A case of renal infection due to *M. gordonae*, progressing from 'sterile' pyuria to hydronephrosis and to severe pyelonephritis has also been described (Pinho et al., 2009).

Two different mycobacterial diseases may occur in the same patient. Koizumi and Sommers (1980) described a patient with culture-positive *M. tuberculosis* 4 years after renal transplantation. The following year, after an episode of transplant rejection treated with methylprednisolone, the patient developed a radiological opacity in the left lower lobe of the lung which, on excision and culture, yielded a heavy growth of *M. xenopi*.

Treatment

Selection of the appropriate drugs for EM depends on the causative organism and on *in vitro* drug sensitivity testing. Unfortunately, however, the results of these tests do not always correlate with clinical response. Owing to its rarity, there is no reliable information on therapy of genitourinary disease due to EM and treatment should therefore be based on drug regimens evaluated for pulmonary and disseminated disease. A 2-year regimen of rifampicin and ethambutol with the addition of either clarithromycin or ciprofloxacin, or both if there is no clinical response after 1 year, is effective for the treatment of disease due to the *M. avium* complex and other slowly growing species (Jenkins et al., 2008).

Treatment of disease caused by the rapid growers is largely based on anecdotal experience. The outcome of therapy is unpredictable and duration of therapy based on clinical response. Therapeutic success has been reported with various combinations of trimethoprim,

doxycycline, amikacin, gentamicin, cephalosporins, imipenem, erythromycin, and the newer macrolides (e.g. clarithromycin) and quinolones (e.g. ofloxacin).

Conclusions

The association of disease of the kidneys and urinary tract with mycobacterial infection is of two kinds. First, mycobacteria (especially members of the *M. tuberculosis* complex) may cause renal and urinary tract disease which, occasionally, leads to a fall in glomerular filtration rate and even end-stage renal disease. Second, patients with advanced renal failure, especially when treated by dialysis or transplantation, are more susceptible both to reactivation of latent mycobacterial disease (usually tuberculosis) or to new infection, especially by EM, but also sometimes tuberculosis. A further association is that patients with certain types of renal disease, notably vasculitis and forms of glomerulonephritis, require treatment with immunosuppressive drugs that render them more susceptible to mycobacterial disease. The development of unexplained fever, malaise, and weight loss in these patients, especially during treatment with immunosuppressive drugs, and in renal transplant recipients, should lead to a suspicion of mycobacterial disease.

Patients with chronic renal failure, including those treated by haemodialysis or peritoneal dialysis, need careful attention to drug dosages when treatment for mycobacterial disease is contemplated. A further complication in renal transplant patients is the interaction between ciclosporin, tacrolimus, and other immunosuppressive drugs, and some of the antibacterial drugs used in the treatment of mycobacterial disease.

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CHAPTER 198

Renal involvement in other infections: diarrhoeal diseases, salmonella, melioidosis, and pregnancy

Raja Ramachandran and Vivekanand Jha

Introduction

The epidemiology, clinical presentation, and pathogenesis of renal involvement in the infections discussed in this chapter have not been not studied extensively. The number of cases is relatively small; and causality is inferred only on the basis of a temporal relationship between the infection and onset of kidney involvement and its resolution following successful treatment of infection (Basu et al., 2011). However, these infections are climate sensitive, and are likely to worsen in coming years as the availability of clean air and safe drinking water are affected by climate change (World Health Organization, 2014). The relationship is easier to establish for acute infections because symptoms force the patient to seek medical attention. In contrast, renal involvement may go unnoticed for long periods in chronic infections. As many of these infections are rarely encountered in the developed world, there is little financial incentive for development of new tests or medications, leading to their inclusion in the list of 'neglected' or 'orphan' diseases. The prevalence, presentation, management, and outcome of kidney involvement in some selected infections are presented in Table 198.1.

Diarrhoea-associated haemolytic uraemic syndrome (D+HUS) typically associated with gastroenteritis caused by *Escherichia coli* O157, or other serotypes, or occasionally *Streptococcus pneumoniae*, is described in Chapter 174.

Post-infectious glomerulonephritis and other glomerulonephritis associated with *Streptococcus* or *Staphylococcus* species and deep-seated infections or endocarditis are described in Chapters 76–79.

Acute kidney injury in community-acquired pneumonia is described in Chapter 243.

Water-borne infections

There is a close linkage between water quality and prevalence of infection-related kidney diseases in the tropics. High ambient temperature and rains lead to soil erosion, which release minerals and organic compounds into flowing water. Warm temperature, humidity, and salinity favour growth of microorganisms, hosts, and vectors (Jha and Parameswaran, 2013). Infections are transmitted by consumption of unsafe drinking water or by entry of organisms through skin and/or mucous membrane secondary to prolonged contact, through working in waterlogged fields or bathing in rivers or ponds. Many of the resultant water-borne diseases and infections are associated with kidney injury. A strong seasonal variation is noted in the prevalence of acute kidney injury (AKI) related to tropical infections, with spikes during and immediately after the rainy season.

Diarrhoeal diseases

Diarrhoeal diseases rank second after respiratory tract infections as the leading cause of infection-related deaths worldwide. Waterborne infections cause diarrhoea by three mechanisms: enterotoxin-mediated necroinflammation (*Vibrio cholera*, entroaggregative/enterotoxigenic *Escherichia coli, Clostridium perfringens, Bacillus cereus, Staphylococcus aureus, Cryptosporidium* spp., *Microsporidia*, and *Cyclospora* spp.), cytotoxic inflammation (*Shigella* spp., *Salmonella* spp., *Campylobacter jejuni*, enterohaemorrhagic/enteroinvasive *E. coli, Klebsiella oxytoca*, and *Entamoeba histolytica*), and by penetrating the intestinal mucosa (*Salmonella typhi* and *Yersinia enterocolitica*).

Renal involvement in diarrhoeal diseases generally presents as AKI due to acute tubular necrosis (ATN) or haemolytic uraemic syndrome (HUS) (Jha and Parameswaran, 2013). Acute tubulointerstitial nephritis (ATIN) and glomerulonephritis are less common. AKI secondary to fluid loss is most common amongst the paediatric population in rural areas and urban slums. The incidence has come down following widespread availability of oral rehydration solutions (Srivastava et al., 1990). The mortality is high in females, infants, and those with dyselectrolytaemias and severe dehydration at admission.

D+HUS typically associated with gastroenteritis caused by *E. coli* O157, or other serotypes, or occasionally *Streptococcus pneumoniae*, is described in Chapter 174. Characteristically the haematological/renal syndrome occurs 5–10 days after the onset of a haemorrhagic,

Table 198.1 Prevalence, presentation, management, and outcome of kidney involvement in selected infections

Organism/disease	Prevalence of renal involvement	Presenting syndromes	Histology	Management	Outcome
Staphylococcus aureus	40–78%[a] 1–4%[b]	AKI RPRF AUA	MsPGN MPGN-I DPGN	Antibiotics	Good
Streptococci	3.9–8.9	AKI RPRF AUA	DPGN	Symptomatic	Excellent
Salmonella typhi	2–3%	AKI RPRF AUA	MsPGN DPGN, AIN, HUS	Antibiotics	Good
Streptococcus pneumoniae	0.4–0.6%[c]	AKI RPRF AUA	MsPGN AIN HUS	No specific therapy	Good; poor with HUS
Campylobacter jejuni *Yersinia enterocolitica*	Rare	AKI RPRF AUA	AIN/ATN DPGN MGN	No specific therapy	Good
Escherichia coli	10–15%[d]	AKI RPRF	ATN/AIN HUS	Supportive therapy/ eculizumab	Good in majority; however, 5–25% develop long-term sequelae
Melioidosis	20%	AKI	ATN/AIN/ Micro abscess	Antibiotics	Prognosis poor with comorbidities/multisystem involvement
Scrub typhus	19–63%	AKI	ATN/AIN MsPGN Focal/DPGN	Antibiotics	Good. Poor if comorbidities/ multisystem involvement
Obstetrical infections	55–83% of obstetric AKI	AKI	ATN RCN	Antibiotics/drainage of septic foci	Poor in dialysis requiring patients

AIN = acute interstitial nephritis; AKI = acute kidney injury; AUA = asymptomatic urinary abnormalities; DPGN = diffuse proliferative glomerulonephritis; HUS = haemolytic uraemic syndrome; IE = infective endocarditis; MsPGN = mesangioproliferative glomerulonephritis; RCN = renal cortical necrosis; RPRF = rapidly progressive renal failure; SN = shunt nephritis.

[a]In patients with infective endocarditis.

[b]In patients with shunt nephritis.

[c]Prevalence of HUS.

[d]10–15% of ST *E. coli* develop HUS.

painful colitis, frequently after the gastrointestinal symptoms have lessened or recovered.

ATIN has been described in association with *Yersinia enterocolitica* (Okada et al., 1991), *Escherichia coli, Pseudomonas aeruginosa*, and *Campylobacter jejuni* infections (Rautelin et al., 1987). Glomerulonephritis has been reported following infection with several enteric pathogens, especially *Campylobacter jejuni* and *Yersinia enterocolitica*. Manifestations include microscopic haematuria, proteinuria, and reduction in glomerular filtration rate (GFR). Kidney biopsy shows endocapillary proliferative glomerulonephritis with or without crescents and membranous nephropathy. Immunofluorescence shows immunoglobulin (Ig)-G deposits along capillary loops and mesangial IgM. One report showed co-localization of deposits with *Yersinia* antigen (Friedberg et al., 1981).

Recurrent, diarrhoeal diseases increase the risk of chronic kidney disease either through multiple episodes of AKI or by worsening other underlying condition, such as nephrolithiasis.

Salmonella typhi and *paratyphi*

Typhoid fever, characterized by fever, headache, abdominal pain, and gastrointestinal symptoms, is a common enteric infection in the tropics. Common complications of typhoid include intestinal perforation, pneumonia, psychosis, encephalitis, and renal involvement.

Renal involvement can take the form of AKI due to dehydration, disseminated intravascular coagulation, intravascular haemolysis in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency, ATIN, or acute glomerulonephritis. Typhoid glomerulonephritis is seen in 2–3% of cases (Buka and Coovadia, 1980), and presents as microscopic haematuria, pyuria, subnephrotic proteinuria, and normal or mildly reduced GFR. Nephrotic syndrome can be seen in patients who also harbour *Schistosoma mansoni* infection. *Salmonella typhi* can be isolated from blood, urine, or stool. Other features include hypocomplementaemia, reduced IgG

and IgM, and elevated IgA levels. Patients with HIV infection may develop simultaneous typhoid hepatitis and glomerulonephritis (Khan et al., 1997, 1998).

Renal biopsy shows mesangioproliferative or diffuse proliferative glomerulonephritis with or without crescents (Indraprasit et al., 1985). Immunofluorescence shows IgA, IgG, and C3, and ultrastructural examination reveals electron dense deposits in the paramesangial area. *S. typhi* Vi antigen can be detected along with immunoglobulins and C3 (Sitprija et al., 1974). Rarely, typhoid fever can cause HUS (Albaqali et al., 2003) (see Chapter 174). Patients with *Schistosoma mansoni* and chronic *S. paratyphi* co-infection who present with nephrotic syndrome show diffuse proliferative glomerulonephritis with mesangial deposits of IgG and IgM.

Glomerular involvement is thought to be secondary to IgA secretion from the lamina propria of the infected gastrointestinal tract resulting in immune complex deposition in glomeruli. Glomerular disease is usually mild, and effective treatment of typhoid resolves most abnormalities. *Schistosoma–Salmonella* co-infection should be treated with ampicillin and niridazole (Bassily et al., 1976). Prognosis depends on multiple factors including malnutrition and the presence of other complications of typhoid fever.

Melioidosis

Melioidosis is caused by a facultative intracellular Gram-negative bacterium, *Burkholderia pseudomallei*. The organism is widely distributed in the environment and is transmitted via percutaneous inoculation, inhalation, aspiration, or ingestion. This disease is encountered mostly during the rainy season in Southeast Asia, Central and South America, and the Caribbean islands amongst workers in paddy fields. Subjects with diabetes mellitus, chronic liver disease, chronic kidney disease, patients receiving immunosuppressive therapy, and heavy alcohol consumers are at increased risk.

Two types of presentation have been described. Genitourinary involvement manifests as suprapubic pain, dysuria, or acute urinary retention. A tender, boggy prostate might be found on examination (Morse, 2009; Zulfikar and Bart, 2012). AKI is noted in about 20% of patients with acute melioidosis septicaemia (Susaengrat et al., 1987). Patients present with fever, cough, tachypnoea, and oliguric renal failure. Hypercatabolism, hypoalbuminaemia, hyponatraemia, jaundice, and multisystem involvement are common accompaniments. Histology may show ATN, microabscesses, or interstitial nephritis. Hypocomplementaemic nephrotic syndrome has also been described (Northfield et al., 2002). The prognosis is poor in patients with co-morbidities, jaundice, and pulmonary involvement, with the mortality approaching 90% in patients with multisystem involvement.

The diagnosis is made by demonstrating the organism in the pus or sputum on Gram stain (bipolar staining with 'safety pin' appearance) and is confirmed by culture in Ashdown's agar containing gentamicin or Ashdown's liquid transport broth containing colistin (Ashdown, 1979). Melioidosis is managed with intravenous ceftazidime (50 mg/kg up to 2 g intravenously (IV) every 6 hours), meropenem (25 mg/kg up to 1 g IV every 8 hours), or imipenem (25 mg/kg up to 1 g IV every 6 hours) for at least 2 weeks followed by oral trimethoprim-sulfamethoxazole for 3 months or more (Leelarasamee and Bovornkitti, 1989).

Acute kidney injury in community-acquired pneumonia

See Chapter 243.

Obstetric infections

Renal involvement may be encountered after unsafe abortion or delivery leading to septic abortion, pyelonephritis, postpartum endometritis, and septic pelvic thrombophlebitis (Chugh et al., 1989; Prakash, 2012). Obstetric causes are the commonest cause of AKI in several parts of the developing world (Bentata et al., 2011, 2012; Chijioke et al., 2012; Ndaboine et al., 2012). The incidence has decreased in some parts of the world following legalization of abortion, wider availability of antibiotics, and adoption of safe delivery practices (Kumar et al., 2006; Prakash et al., 2006; Prakash, 2012).

The most common organism responsible for septic abortion complicated by AKI is *Clostridium* spp. Presentation is with high-grade fever, chills and rigor, abdominal pain, prolonged or heavy vaginal bleeding, with foul-smelling discharge and backache. As sepsis sets in, patients develop hypothermia, hypotension, and multiorgan failure. Management includes supportive therapy, fluids, and antibiotics along with aggressive source control with evacuation of retained products of conception. Renal function usually recovers, but about 15% of patients develop renal cortical necrosis.

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