21.10.8 Infection- associated nephropathies 5034 A

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section 21 Disorders of the kidney and urinary tract 5034 sickle haemoglobinopathies. This is highly aggressive, can occur in children as young as 2 years of age, and, so far, has proved to be uni- versally fatal within 2 years of presentation. Albuminuria and proteinuria The appearance of abnormal levels of albumin in the urine is an early manifestation of SCN. It is present in some teenage children but its prevalence increases with age, reaching approximately 60% in adults over 45 years. For many, the degree of albuminuria appears not to progress, but in others, nonselective proteinuria develops rapidly, and these are the patients most at risk of future renal impairment. Rarely, patients can develop full-blown nephrotic syndrome, though this should always be investigated to rule out a second pathology. In particular, nephrotic syndrome has been reported in a number of pa- tients following infection with human parvovirus B19, in which case renal biopsy demonstrates the collapsing form of focal segmental glomerulosclerosis and (if taken early in the disease course) occasion- ally positive staining for the HPV B19 virus. In such cases the neph- rotic syndrome is usually self-limiting, although a gradual decline in renal function often occurs in the months and years following the acute event. Treatment options Therapies to prevent progression of chronic kidney disease Treatment of patients with proteinuria with inhibitors of the renin–angiotensin system to reduce glomerular pressure and proteinuria has become accepted as standard practice in those who can tolerate it from a blood pressure and serum potassium perspective. Intermittent or regular blood transfusion is often used to manage the acute com- plications of SCD or for primary or secondary prevention of stroke, but there is little evidence for its use in the prevention or treatment of SCN. However, using blood transfusion to reduce the percentage of sickle haemoglobin in patients prior to surgery does have proven benefits and this is likely to be particularly important in those under- going renal transplantation. Hydroxycarbamide (hydroxyurea) therapy has clear clinical benefits for many patients with SCD, including a reduction in hospitalization episodes and painful crises. Although studies have failed to demonstrate any

clear benefit of this treatment in the short term, it is likely that it helps maintain kidney health in those who respond well to this therapy in other respects. Haematopoietic cell transplantation is the only curative treatment currently available for SCD and is usually reserved for children with major complications such as stroke. Although it is probable that re- cipients of such transplants who have a good outcome are protected from developing SCN in future, most published studies exclude those with established renal disease from receiving this treatment and so its role in treating kidney dysfunction has not yet been studied. Treatment of endstage kidney disease Despite optimal treatment, some patients with SCD will develop progressive kidney failure that will eventually necessitate the need for renal replacement therapy. The prognosis for patients with SCD on dialysis is poor and the average lifespan after a diagnosis of endstage kidney disease is only 4 years. Kidney transplantation offers a better outcome and can increase life expectancy to 10 to 15 years in those who have a well-functioning graft. Recurrent SCN can complicate the outcome following transplantation, although this can be mitigated by placing the patient on an exchange trans- fusion programme. FURTHER READING Alvarez O, et al. (2012). Effect of hydroxyurea treatment on renal func- tion parameters: results from the multi-center placebo-controlled BABY HUG clinical trial for infants with sickle cell anemia. Pediatr Blood Cancer, 59, 668–74. Derebail VK, et al. (2019). Progressive Decline in Estimated GFR in Patients With Sickle Cell Disease: An Observational Cohort Study. Am J Kidney Dis, pii: S0272-6386(19)30007-1. doi: 10.1053/j. ajkd.2018.12.027. Nath KA, Hebbel RP (2015). Sickle cell disease: renal manifestations and mechanisms. Nat Rev Nephrol, 3, 161–71. Sharpe CC, Thein SL (2014). How I treat renal complications in sickle cell disease. Blood, 24, 3720–6. Thompson J, et al. (2007). Albuminuria and renal function in homo- zygous sickle cell disease: observations from a cohort study. Arch Intern Med, 167, 701–8. 21.10.8 Infection-associated nephropathies A. Neil Turner ESSENTIALS Infection may be a primary cause of renal disease (e.g. postinfectious glomerulonephritis) or affect the kidneys on a background of debilitating illnesses and previous medical interventions. Renal dis- ease may arise as a consequence of immune responses to a pathogen, direct invasion by the microorganism, or the effects of infection on the systemic or local circulations. Table 21.10.7.1 Signs and symptoms of renal involvement in sickle cell disease Initial changes (>80% patients) Early signs of renal damage (30–60% of patients) Markers of progressive disease (10–20% patients) Increased glomerular filtration rate Microalbuminuria Nonselective proteinuria Hyposthenuria Haematuria Falling glomerular filtration rate (>5 ml/min per 1.73 m2 per year) Nocturia/enuresis Tendency to hyperkalaemia Falling steady state haemoglobin concentrationa a Due to falling endogenous erythropoietin production as renal function declines.

21.10.8 Infection-associated nephropathies 5035 Glomerulonephritis—associated with chronic and acute bacterial infections. Shunt nephritis follows colonization of a ventriculoatrial shunt, most commonly with Staphylococcus epidermidis, leading to constitutional symptoms, an acute inflammatory response, and (most characteristically) a type 1 mesangiocapillary glomerulonephritis. Infective endocarditis and other deep-seated bacterial infections may produce a similar renal picture, but they can also mimic vascu- litic syndromes and outcome is dependent on the response of the infection to treatment. Acute postinfectious glomerulonephritis—see Chapter 21.8.5. Interstitial nephritis—bacteria that can cause this include leptospira (Weil's disease), Rickettsia rickettsii (Rocky Mountain spotted fever), legionella, and mycobacteria. Viral infections include hantaviruses (haemorrhagic fever with renal syndrome and nephropathia epidemica) and, almost exclusively following renal transplantation, cytomegalovirus and polyomavirus hominis type 1 (BK) virus. HIV-associated renal disorders—these include HIV nephropathy, which is a focal

segmental glomerulosclerosis of ‘collapsing’ form, occurring almost exclusively in black patients. Other morpholo- gies are more common in other races, but interstitial disease is also common as a manifestation of infection or of drug toxicity. Hepatitis B virus—chronic infection is strongly associated with membranous nephropathy; affected individuals are HBeAg and HBsAg positive, usually with coexistent hepatitis; seroconversion from HBeAg positive to HBeAb positive (naturally or induced by treatment) is associated with remission of the renal lesion. Hepatitis C virus—chronic infection is the commonest cause of mixed essential (type II) cryoglobulinaemia in most populations; it is associated with membranoproliferative glomerulonephritis (MPGN, also described as MCGN), and reduction of viral replication has been associated with disease remission.
Introduction Almost all renal lesions, particularly glomerular lesions, may be asso- ciated with infections. In the developed world, infection-associated nephritis was once predominantly recognized during acute infec- tions occurring in apparently healthy individuals, and this is still the pattern in many countries. However, improvements in living con- ditions and health care reduce the numbers of healthy people suc- cumbing to complications of infection. Instead, infections occurring on a background of debilitating illnesses and previous medical inter- ventions become more common precipitants of renal disease. In this chapter, glomerular diseases and interstitial diseases as- sociated with infection are considered in turn. Particular attention is given to those glomerulopathies associated with bacterial endo- carditis and other chronic bacterial infections, and three viral in- fections of worldwide importance, HIV, hepatitis B, and hepatitis C. Pathogenesis Infection-associated glomerular disease is usually attributed to trapping of circulating antigen–antibody complexes in the glom- erulus, or to immune responses to pathogen-derived antigens that become ‘planted’ in the glomerulus. The evidence for deposition of circulating immune complexes is strong for cryoglobulinaemia, and highly plausible for infections occurring within the vascular system such as bacterial endocarditis. In most other infections the evidence is less clear, and this is probably not a common mechanism of glomerular disease. A direct cytopathic effect on glomerular cells seems likely for some pathogens such as HIV and parvovirus, both of which infect glomerular podocytes and have been associated with ‘collapsing’ focal segmental glomerulosclerosis (FSGS). Interstitial renal disease is often blamed on direct invasion by the microorganism, and for some there is evidence that this is true. The pathogen may cause injury directly, or indirectly by causing cells to express foreign antigens which generate an immune response. More speculatively, an immune response generated to an organism may cross-react with a remote self-antigen, triggering autoimmunity through molecular mimicry, but there are no unequivocal examples of this. Infection may also involve the kidney by interfering with the cir- culation either generally (septic shock) or locally (e.g. by causing thrombotic microangiopathy, as for Escherichia coli O157 or Capnocytophaga canimorsus (previously DF-2)). Occasionally, toxins may be released that harm the kidney directly (e.g. haemo- globin in malaria). Medically administered toxins include anti- microbial agents that impair renal function by crystallization (e.g. aciclovir, indinavir) or by predictable toxicity (e.g. aminoglycosides, amphotericin, and tenofovir), or by idiosyncratic reactions such as acute interstitial nephritis (e.g. penicillins). Glomerulonephritis associated with chronic
and acute bacterial infections Classic acute postinfectious glomerulonephritis is considered in Chapter 21.8.5. This account considers subacute or chronic dis- eases, although other causes of a ‘classic’ picture are mentioned. Shunt nephritis was first recognized in the 1960s, and it remains the archetype of an immune complex nephritis. The glomerulonephritis occurring in association with infective endocarditis is very similar. Both are caused by subacute infection within the bloodstream, with constant shedding of antigen and formation of antigen–antibody complexes.

Other bacterial infections may cause similar pictures. Shunt nephritis and similar syndromes of intravascular infection In shunt nephritis, a ventriculoatrial shunt implanted for hydro- cephalus becomes colonized by bacteria, usually of low pathogen- icity. More common modern equivalents are infected long-term central venous catheters and other intravascular devices. The syn- drome does not occur with ventriculoperitoneal shunts, which are therefore now the preferred neurosurgical option, making shunts now a rare cause of the syndrome. Although Staphylococcus epi- dermidis has been most commonly implicated in these infections, Propionibacterium acnes or other organisms are sometimes in- volved. Typically the diagnosis is only appreciated after weeks to months of symptoms of mild to moderate pyrexia and malaise as- sociated with haematuria and proteinuria and progressive renal impairment. Fevers have often been attributed to urinary infec- tion in patients with neurogenic bladders. There may be moderate splenomegaly. Investigations show complement consumption and

 an acute-phase response with normochromic normocytic anaemia, and variable renal impairment. The renal lesion is characteristically a type 1 membranoproliferative (mesangiocapillary) glomeruloneph- ritis with deposition of multiple immunoglobulins and complement components beneath the endothelium, the classic appearance of a circulating immune complex nephritis. Sometimes the picture is more severe, showing a diffuse proliferative lesion, occasionally with crescents. In other cases, the histological appearances are less pro- nounced with focal proliferative changes. Antibiotic treatment alone is almost never adequate to cure these infections, which require removal of the intravascular device, fol- lowed by its replacement after an interval if it is still required. Delayed diagnosis and delayed removal may lead to more severe and irreversible renal damage, and sometimes to endstage renal failure, but some degree of recovery can follow successful treatment. Infective endocarditis A similar syndrome can occur in infective endocarditis, as part of which minor degrees of glomerular disease are probably extremely common. In truly subacute endocarditis, symptoms and signs are as seen in shunt nephritis. Typical streptococcal infections are well represented in case reports, but there have been multiple reports involving ‘slow’ infections such as Q fever (Coxiella burnetii), and more unusual causes including chlamydia and fungi. Typical patients in developed countries have shifted from being young patients with rheumatic heart disease, to being elderly with comorbid conditions, long-term vascular access devices, pace- makers, etc. Infection of prosthetic or native heart valves may be implicated. Right-sided endocarditis occurring in intravenous drug abusers may be particularly likely to present as nephritis, because the diagnosis is often delayed. Depletion of serum complement is again diagnostically useful, but, as for shunt nephritis, most other serological and haemato- logical changes are nonspecific. Partial treatment with antibiotics makes diagnosis and management more difficult, as positive blood cultures are usually a key part of proving the diagnosis and selecting appropriate therapy. The pathological lesion is typically similar to that of shunt neph- ritis, but forms of endocarditis that are acute, rather than subacute (e.g. that associated with Staphylococcus aureus), are more likely to cause glomerulonephritis in a diffuse proliferative pattern, some- times with crescent formation. Focal changes that are indistinguish- able from antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis have been reported in the literature, and ANCA are de- tected in some patients. There may be a florid purpuric cutaneous vasculitis (as in Fig. 21.10.8.1), but there may be few or no other signs of vasculitis elsewhere. However, immune deposits are usually pre- sent in glomeruli, in contrast to the primary small-vessel vasculitides. In most cases, the outcome is dependent on the response of the endocarditis to

treatment, but renal involvement is a poor prog- nostic factor for survival, which may be simply because it reflects long-lasting infection, although recovery from dialysis dependence may occur. Patients with endocarditis are also prone to two other renal le- sions: interstitial nephritis related to antibiotics and, in those with disease on the left side of the heart or with right–left shunts, renal emboli, although glomerulonephritis is a more common cause of urinary abnormalities. Deep-seated bacterial infections Amyloidosis is a well-recognized consequence of very chronic bac- terial (including mycobacterial) and other infections, and is de- scribed in Chapters 12.12.3 and 21.10.5. As in reactive amyloidosis of other aetiologies, progression of the renal lesion may be prevented or even partially reversed by treatment of the cause. Deep-seated infections, particularly abscesses, may also be asso- ciated with glomerulonephritis. Although the mechanisms involved are presumably similar to those of shunt nephritis and nephritis as- sociated with endocarditis, blood cultures have often been negative in reported cases. Staphylococcus aureus is the most frequently impli- cated organism. A wide variety of renal lesions have been described, usually inflammatory/proliferative and with immunoglobulin de- position. Unsuspected abscesses or other deep-seated infections are occasionally found only after the renal biopsy appearances trigger a search. Such hidden abscesses are more likely in obese or older people, and in those on corticosteroids or who are immunosup- pressed by other means or by disease. Acute glomerulonephritis and other infections Acute glomerulonephritis resembling poststreptococcal neph- ritis has been reported in association with a large number of other organisms, including current (as opposed to recent) infection with staphylococci, streptococci, and other bacteria, and with acute viral infections that are usually self-limiting. These include Epstein–Barr virus, cytomegalovirus, varicella, measles, mumps, parvovirus, and coxsackieviruses. Some may cause a clinical syn- drome that is very similar to poststreptococcal nephritis, while others typically cause a less florid ‘nephritic’ or mixed ‘nephritic/ nephrotic’ picture. Staphylococcus aureus is particularly asso- ciated with a variant of postinfectious glomerulonephritis with prominent nephrotic features and dominant IgA deposition in glomeruli. Diagnostic difficulties in bacterial infection-related glomerulonephritis Infection-related nephritis may present in a very similar manner to nephritis associated with other systemic diseases, notably microscopic polyangiitis and other small-vessel vasculitides (see Fig. 21.10.8.1 Cutaneous vasculitis in a patient with Staphylococcus aureus endocarditis.

 Chapter 21.10.2). As both types of disease process may be associated with fever, a systemic illness, and an acute-phase response, it is im- portant to consider the possibility of infection in all patients thought to have systemic vasculitis. Blood cultures should be routine. ANCA assays are extremely useful, but it is important to note that ANCA positivity has been recorded in many infections, both by fluorescence and by solid-phase assays: ANCA are not diagnostic of small-vessel vasculitides. Renal biopsy is often the most discriminating investi- gation. Infection-associated glomerulonephritis is usually (but not invariably) associated with plentiful immunoglobulin deposition, whereas small-vessel vasculitis is characteristically pauci-immune. Nonglomerular causes of renal impairment (interstitial nephritis, acute tubular necrosis) are also distinguished by renal biopsy. Interstitial nephritis associated with infections Bacterial infections Acute bacterial pyelonephritis is usually a florid and painful dis- order associated with symptoms of urinary tract infection, as de- scribed in Chapter 21.13. Substantial renal impairment is usual only if a single functioning kidney is affected. Occasionally, however, the diagnosis is masked by immunosuppression (e.g. in a transplanted kidney), age, or other factors, and the diagnosis is made by the renal biopsy appearances of neutrophils in the

interstitium and in tubules, which are rarely found in any other renal lesions. Acute interstitial nephritis is a key feature of Weil’s disease, a se- vere form of leptospirosis (see Chapter 8.6.35). Jaundice and renal failure follow a febrile illness caused by infection with Leptospira interrogans. The renal lesion comprises interstitial oedema with pre- dominantly mononuclear infiltrates and foci of tubular necrosis. Renal failure is usually oliguric but may be polyuric. Dialysis may be required for days to weeks, and renal recovery may sometimes be incomplete. Other bacterial infections that may cause a similar pathological picture include Rocky Mountain spotted fever (Rickettsia rickettsii), in which there may be an interstitial nephritis with foci of haemor- rhage, and acute Yersinia pseudotuberculosis infection, in which an acute lymphocytic interstitial nephritis has been described in sev- eral patients. Legionnaires’ disease (Legionella pneumophila) has been reported to be associated with renal impairment, also with an interstitial nephritis, but in some instances may show a picture of acute tubular necrosis. The same is probably true of other severe pneumonias. Mycobacteria can cause a chronic granulomatous interstitial nephritis (discussed in ‘Mycobacteria’). Viral infections Hantaviruses Hantaviruses are carried by small rodents, and have been associ- ated with a range of human syndromes that involve the kidneys with varying severity. ‘Haemorrhagic fever with renal syndrome’ (HFRS) is characterized by oliguric renal failure, associated histologically with lymphocytic interstitial nephritis that may be haemorrhagic in severe cases, reflecting the systemic bleeding diathesis. Some pa- tients have been reported to have persistent renal impairment after recovery. HFRS was originally associated with Hantaan strains of hanta- virus in Korea, while milder disease, with less frequent and usually less severe renal impairment and without haemorrhagic diathesis, was associated with the Seoul strain. Milder disease (nephropathia epidemica) recognized in northern Europe and subsequently more widely was associated with the Puumula strain. However, it has be- come apparent that there are many more subtypes of hantavirus, and the association of a serotype with a particular clinical picture is not rigid. Severe disease with shock, variable haemorrhage, and some- times pulmonary impairment has been encountered in the Balkans and Greece. Disease with predominantly pulmonary manifestations and shock has been recognized, particularly in North America, al- though these geographical variations in clinical picture are no more rigid than the strain variations. Ribavirin is active against hantaviruses in vitro, and therapy with ribavirin was found to be effective in HFRS caused by the classic Hantaan strain in China and confirmed in Korea, but there are likely to be strain differences as no benefit could be demonstrated in trials in the pulmonary syndrome in North America, and evidence for value more widely seems weak. Cytomegalovirus, polyomaviruses, and other viruses Cytomegalovirus (CMV) may lie dormant in renal tubular cells, and during new or reactivated infection causes characteristic in- clusion bodies. This rarely has a significant impact on renal func- tion outside the setting of renal transplantation, where CMV infection commonly occurs concurrently with acute rejection. Although there is evidence that CMV infection may precipitate rejection, it is also clear that the risk of CMV infection is greatly increased by most types of antirejection therapy. CMV may also rarely cause a florid glomerular lesion characterized by gross endo- thelial cell damage and swelling, resembling pre-eclampsia. This has again been recognized almost exclusively in renal transplants, where some believe that the appearances are due to, or complicated by, vascular rejection. Human polyomaviruses (BK and JC) were previously believed to be benign passenger viruses which replicated without causing damage during immunosuppression. However, BK virus has been increasingly recognized as a cause of impaired renal transplant function, usually many months after transplantation. The histo- logical changes of tubulitis closely resemble acute cellular rejection, but further immunosuppression favours further infective damage. Observation of typical inclusion bodies and immunohistochemical studies prove the true cause of

the tubulitis, and renal function may improve after reduction of immunosuppressive agents, although renal outcome is often poor despite this. Polymerase chain reaction-based screening has been introduced in many centres in attempts to make an earlier diagnosis, but there is still no proven antiviral therapy and reduction of immunosuppression is not without risk. A strategy of combining leflunomide (as a replace- ment for azathioprine or mycophenolate mofetil), intravenous immunoglobulin, and ciprofloxacin has been tried, but shown no benefit. Polyomavirus renal disease seems to be less common in pa- tients immunosuppressed for reasons other than renal transplant- ation, but it is being increasingly recognized. A wide range of other viruses and microorganisms have been less regularly associated with interstitial lesions. HIV (considered in the following section) may cause an interstitial nephritis. Another

 condition that is likely to be infective in origin, Kawasaki's disease, is associated with interstitial nephritis, although glomerular lesions have also been described occasionally. HIV and renal disease Renal impairment is commonly encountered at some stage of HIV infection. The largest single cause of serious renal disease in this group is the distinct entity of HIV nephropathy. However, this gen- eralization is misleading as this specific diagnosis is largely restricted to black patients, and there are many other causes of renal disease in patients with HIV infection. FSGS associated with HIV infection (HIV nephropathy) HIV nephropathy is characterized by heavy proteinuria and renal impairment. It is an important cause of endstage renal failure in Africa, but also significant in black adults of working age in the United States of America. Although it has often been described as an initial manifestation of HIV infection, in these circum- stances the infection is advanced, with high viral loads and low CD4 counts. Histologically, the appearances are of FSGS of the 'collapsing' form, with injury and hypertrophy of glomerular epithelial cells accompanied by variable interstitial inflamma- tion with oedema and microtubular dilatation (Fig 21.10.8.2). The racial (black African) restriction of susceptibility to HIV nephropathy and increased risk of other types of FSGS is due to variants in the APOL1 gene which convey resistance to trypano- somiasis. How they produce their disadvantageous renal effects is not yet known. Without therapy the condition progresses to endstage renal failure rapidly, over weeks to months. Perhaps because it is associated with low CD4 counts, the medium-term prognosis in the past was poor despite renal replacement therapy, but effective antiviral therapy can alter this. Non-FSGS nephropathies in HIV infection FSGS accounts for a minority of HIV-associated renal disease in most populations. An HIV immune complex glomerulonephritis (HIVICK) has been described, but so have other specific types of renal disease, encompassing almost all types of glomerular le- sion, interstitial nephritis, cryoglobulinaemia, and thrombotic microangiopathy. IgA nephropathy has been frequently recorded. Some of these lesions may be directly caused by HIV infection, while others are related to concurrent infections with other microorganisms, and some may be related to therapy. The occur- rence of autoimmune phenomena in HIV infection may also be accompanied by an increase in immune-mediated primary renal diseases of many types. Interstitial nephritis is often but not always related to anti-HIV drugs. Tenofovir in particular may cause tubular injury with renal impairment and sometimes Fanconi's syndrome. Aciclovir and indinavir have replaced sulphonamides as common causes of crystal nephropathy. Adjusting the doses of these and other drugs in the setting of renal impairment is prob- lematic. Patients with HIV infection receive many other drugs with predictable nephrotoxicity, and polypharmacy also puts them at risk of allergic reactions. Highly active antiretroviral therapy and

other therapies Highly active antiretroviral therapy (HAART), when instituted early, may arrest the

progression of FSGS as well as lowering the mortality of patients with endstage renal failure. Severity of chronic damage on biopsy may be a better prediction of prognosis than serum creatinine. Its effect on non-FSGS nephropathies may also be beneficial. Patients with any diseases associated with proteinuria should be treated with angiotensin-converting enzyme inhibitors. Treatment with corticosteroids should probably be considered in patients with HIV-FSGS who progress despite effective HAART and intensive renoprotective therapy with angiotensin-converting enzyme inhibi- tors and blood pressure control. Patients with good control of HIV do well on renal replacement therapies, and several national guidelines now allow and recom- mend transplantation for patients whose prognosis is of many years. In high-incidence regions, transplantation of kidneys from HIV- positive donors improves organ supply. Nephropathy associated with hepatitis B virus Chronic infection with hepatitis B virus (HBV) (see Chapter 8.5.21) is strongly associated with membranous nephropathy, and it is an important secondary cause of the lesion. A less clear relationship holds with membranoproliferative glomerulonephritis (MPGN, also known as MCGN), while for hepatitis C virus (HCV) the con- verse is true. Chronic HBV infection is much more common in some regions and racial groups, and the distribution of HBV-related nephropathy closely follows this distribution. The clinical picture may be compli- cated by the concurrence of HBV infection by infection with HCV, HIV, or with other organisms, or by the coincidence of significant renal and hepatic disease. HBV membranous nephropathy has a Fig. 21.10.8.2 Histology of HIV-associated nephropathy showing glomerular collapse with a focal sclerosing lesion, microcystic tubular dilatation, and interstitial inflammation (magnification ×200). Reproduced with permission from Naicker S, Paget G. HIV and renal disease. In: Turner N, Lameire N, Goldsmith DJ, et al. Oxford Textbook of Clinical Nephrology. 4th ed. Oxford: Oxford University Press (2015). Courtesy of Prof Stewart Goetsch, University of the Witwatersrand.

 close relationship with virus multiplication, so affected individuals are usually HBeAg and HBsAg positive, with evidence of hepatitis, although this may be minor. Membranous nephropathy is a more common complication of HBV infection in children, but it is also more benign in this group. The lesion may be static, or in some cases (particularly in adults) associated with progressive deterioration to endstage renal failure. Histopathology is typical of membranous nephropathy, and HBV antigens may be detectable in glomerular deposits. Idiopathic membranous nephropathy is caused by autoantibodies to podocyte surface proteins, usually to the phospholipase A2 (PLA2) receptor, but these are not typically identified in patients with secondary membranous nephropathy, including that associated with HBV. The target in these circumstances may be viral, but it has not been identified. Seroconversion from HBeAg positive to HBeAb positive is asso- ciated with remission of the renal lesion, whether the conversion oc- curs naturally or is induced by treatment. Spontaneous remission of the renal lesion is more likely in children. Antiviral treatment is the appropriate therapy when required, as immunosuppression may increase viral burden. Recently acquired (within months) HBV infection has been asso- ciated with classic polyarteritis nodosa (PAN) in some populations, such as in France and North America, but even in these areas HBV- PAN is uncommon and apparently decreasing. Furthermore, the as- sociation of the two diseases is rare in some countries with low (e.g. the United Kingdom) and with high (e.g. Thailand) rates of HBV carriage, suggesting the involvement of a cofactor. Clinically, the disease is typical of PAN, affecting medium and somewhat smaller vessels but not capillaries, and therefore not usually associated with focal necrotizing or crescentic nephritis. ANCA are not usually detected. Treatment is difficult to balance as immunosuppression (usually with corticosteroids alone) is often indicated, but favours viral

replication and exacerbation of liver disease, while remission is associated with seroconversion from HBeAg positivity to HBeAb positivity. Nephropathy associated with hepatitis C virus Chronic HCV (see Chapter 8.5.22) infection is the commonest cause of mixed essential (type II) cryoglobulinaemia in most populations, and an important cause of MPGN without overt cryoglobulinaemia. The clinical picture includes cutaneous vasculitis, glomerular path- ology (mesangiocapillary glomerulonephritis, MCGN), and other manifestations. Cryoglobulins contain quantities of HCV antigens and bound antibody, in addition to monoclonal IgM rheumatoid factors. HCV may also be associated with MCGN in the absence of detectable cryoglobulins. A relationship with membranous neph- ropathy is also possible, but not proven. As for HBV, reduction of viral replication has been associated with disease remission. Immunosuppression with corticosteroids and some- times other agents may be required to control disease manifestations caused by vasculitis. B-cell depletion with anti-CD20 monoclonal anti- bodies may help to control the disease if antiviral therapy does not. Renal sequelae of other chronic infections Amyloidosis Amyloidosis (see Chapter 12.12.3) may be a consequence of all sorts of chronic infection, but of the ‘tropical’ infections is most frequently associated with schistosomiasis, filariasis, or leishmaniasis. Mycobacteria Mycobacterial infections (see Chapter 8.6.26) cause a chronic granu- lomatous interstitial nephritis that is characteristically associated with inflammatory and fibrotic abnormalities in the ureters and lower (a) (b) (c) Fig. 21.10.8.3 Radiological appearances in urinary schistosomiasis. (a) Plain radiograph showing linear bladder calcification. (b) Retrograde urogram showing contracted bladder with reflux into extremely dilated ureter, and hydronephrosis. (c) Cystogram showing large irregular filling defect in the bladder caused by a tumour. Reproduced with permission from Barsoum RS. Schistosomiasis. In: Turner N, Lameire N, Goldsmith DJ, et al. Oxford Textbook of Clinical Nephrology. 4th ed. Oxford: Oxford University Press (2015). Copyright © 2015 Oxford University Press.

 urinary tract. Symptoms often relate to lower tract involvement, but the disease may be asymptomatic, and in the earliest stages involvement is presumed to be restricted to the kidneys, with subsequent spread to the lower tract. Sterile pyuria is the rule, and impaired renal function is common at presentation. Imaging by intravenous urography or other techniques will show blunting of calyces, progressing to changes typ- ical of pyelonephritis or papillary necrosis, along with lower tract ab- normalities such as ureteric strictures and scarring and contraction of the bladder. Amyloidosis is a well-recognized secondary complication of mycobacterial infections. Idiosyncratic reactions to antituberculous drugs are another common cause of late renal dysfunction. Syphilis Congenital syphilis (see Chapter 8.6.37) may cause severe nephrotic syndrome with the histological pattern of membranous nephropathy. This is also the usual pattern when secondary syphilis rarely causes nephrotic syndrome. Both respond to antispirochaetal treatment. Malaria Plasmodium falciparum infections (see Chapter 8.8.2) are an ex- tremely important cause of acute kidney injury worldwide. This oc- curs in 1 to 5% of infected patients native to a malarial area, but a higher proportion of nonimmune visitors, and is associated with high mortality (15–45%). Series from Africa have cast doubt on the existence of a specific chronic malarial nephropathy that was described in earlier litera- ture. Biopsy studies have shown a high incidence of infection-related glomerulonephritis and of FSGS, but have found little evidence of a distinct malarial disease. Schistosomiasis Schistosomiasis (Fig. 21.8.10.3; see Chapter 8.11.1) is best recog- nized for causing disease of the lower urinary tract, but chronic in- fections associated with hepatosplenomegaly may be associated with glomerular disease after many years. In Schistosoma haematobium infection this is often due to secondary infections with Salmonella spp. rather than

directly associated with schistosomal infection. In Schistosoma mansoni infection the relationship is probably usually directly causal, typically causing MPGN. Filariasis Longstanding filariasis (see Chapter 8.9.2) may also be associated with glomerular lesions. An acute syndrome with tubulointerstitial nephritis has also been described in association with the presence of microfilariae in renal capillaries. FURTHER READING Arendse CG, et al. (2010). The acute, the chronic and the news of HIV- related renal disease in Africa. Kidney Int, 78, 239–45. Bigé N, et al. (2012). Presentation of HIV-associated nephropathy and out- come in HAART-treated patients. Nephrol Dial Transplant, 27, 1114–21. Bonarek H, et al. (1999). Reversal of c-ANCA positive mesangiocapillary glomerulonephritis after removal of an infected cysto-atrial shunt. Nephrol Dial Transplant, 14, 1771–3. Clementi A, et al. (2011). Renal involvement in leishmaniasis: a review of the literature. Nephrol Dial Transplant Plus, 4, 147–52. Conlon PJ, et al. (1998). Predictors of prognosis and risk of acute renal failure in bacterial endocarditis. Clin Nephrol, 49, 96–101. Daugas E, Rougier JP, Hill G (2005). HAART-related nephropathies in HIV-infected patients. Kidney Int, 67, 393–403. De Vita S, et al. (2012). A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. Arthritis Rheum, 64, 843–53. Doe JY, et al. (2006). Nephrotic syndrome in African children: lack of evidence for ‘tropical nephrotic syndrome’? Nephrol Dial Transplant, 21, 672–6. Elsheikha HM, Sheashaa HA (2007). Epidemiology, pathophysiology, management and outcome of renal dysfunction associated with plasmodium infection. Parasitol Res, 101, 1183–90. Fabian J, et al. (2013). The clinical and histological response of HIV- associated kidney disease to antiretroviral therapy in South Africans. Nephrol Dial Transplant, 28, 1543–54. Genovese G, et al. (2010). Association of trypanolytic ApoL1 variants with kidney disease in African-Americans. Science, 329, 841–5. Haffner D, et al. (1997). The clinical spectrum of shunt nephritis. Nephrol Dial Transplant, 12, 1143–8. Krautkrämer E, Zeier M, Plyusnin A (2013). Hantavirus infection: an emerging infectious disease causing acute renal failure. Kidney Int, 83, 23–7. Lai AS, Lai KN (2006). Viral nephropathy. Nat Clin Pract Nephrol, 2, 254–62. Majumdar A, et al. (2000). Renal pathological findings in infective endocarditis. Nephrol Dial Transplant, 15, 1782–7. Montseny JJ, et al. (1995). The current spectrum of infectious glom- erulonephritis: experience with 76 patients and review of the litera- ture. Medicine (Baltimore), 74, 63–73. Moudgil A, et al. (2001). Association of parvovirus B19 infection with idiopathic collapsing glomerulopathy. Kidney Int, 59, 2126–33. Muller E, Kahn D, Mendelson M (2010). Renal transplantation between HIV-positive donors and recipients. N Engl J Med, 362, 2336–7. Naqvi R, et al. (2003). Outcome in severe acute renal failure associated with malaria. Nephrol Dial Transplant, 18, 1820–3. Nasr SH, et al. (2008). Acute postinfectious glomerulonephritis in the modern era: experience with 86 adults and review of the literature. Medicine (Baltimore) 87, 21–32 Neugarten J, Baldwin DS (1984). Glomerulonephritis in bacterial endocarditis. Am J Med, 77, 297–304. Nickeleit V, Mihatsch MJ (2006). Polyomavirus nephropathy in na- tive kidneys and renal allografts: an update on an escalating threat. Transpl Int, 19, 960–73. Perico N, et al. (2009). Hepatitis C infection and chronic renal diseases. Clin J Am Soc Nephrol, 4, 207–20. Peters CJ, Simpson GL, Levy H (1999). Spectrum of hantavirus infec- tion: hemorrhagic fever with renal syndrome and hantavirus pul- monary syndrome. Ann Rev Med, 50, 531–45. Post FA, et al. (2008). Predictors of outcome in HIV-associated neph- ropathy. Clin Infect Dis, 15, 1282–9. Sneller M, Hu Z, Langford C (2012). A randomized controlled trial of rituximab following failure of antiviral therapy for hepatitis C virus- associated cryoglobulinemic vasculitis. Arthritis Rheum, 64, 835–42. Turner AN, et al. (eds) (2015). Oxford textbook of clinical nephrology, 4th edition. Chapters 183–198 and 284. Oxford University Press, Oxford. Watts RA, Scott DG, Mukhtyar C (2015). Secondary vasculitis. In: Vasculitis in clinical practice, pp. 173–84. Springer International Publishing AG, Cham. Wearne N, et al. (2012). The spectrum of renal histologies seen in HIV with outcomes, prognostic indicators and clinical correlations. Nephrol Dial Transplant, 27, 4109–18.

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