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the tubular cells in addition to the interstitial changes. Historical perspective In 1898, Councilman described the first accounts of acute tubulointerstitial nephritis involving patients with scarlet fever or diphtheria, whose kidneys were sterile but had inflammatory infiltrates. Since then, drug-induced AIN has surpassed infec- tion as a more common cause of the condition in adults, espe-cially with the widespread use of antibiotics and proton pump inhibitors. Aetiology, pathogenesis, and pathology The aetiology is divided into groups such as drugs, infections, and immune-based causes. See Box 21.9.1.1. Drugs Medications are now responsible for 70 to 90% of cases of AIN. It is important to remember that any drug can cause this condition, es- pecially with the flood of new agents entering the formulary. The commonly recognized drugs implicated in causing AIN in- clude proton pump inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), penicillins, cephalosporins, sulfa-based agents, and frusemide (furosemide). Unexpected culprits include cocaine and Chinese herbal agents. The proton pump inhibitors have been recognized as causing AIN since 1992. They have been shown to induce AIN on rechallenge, behave as a class effect rather than due to specific drugs within the group, and are now the most common cause of drug-induced AIN. 21.9 Tubulointerstitial diseases

section 21 Disorders of the kidney and urinary tract 4952 Infections Many pathogenic organisms (bacterial, viral, protozoal, and fungal) have been implicated as causing AIN, and in children, infection re- mains the most common cause of this condition: • Streptococcal—what was a very common aetiology has now waned with the advent of and widespread use of antibiotics. • Legionella—although a relatively rare cause of AIN, the organism can be detected in renal tissue by immunofluorescence and electron microscopy. Coexistent rhabdomyolysis may be present. • HIV—AIN is present in up to 40% of autopsy series. HIV can also cause a glomerulonephritis in addition to a mononuclear cell in- filtrate of predominantly CD8+-positive lymphocytes. • Epstein–Barr virus—renal involvement is not uncommon. CD8+ T lymphocytes may predominate. • Cytomegalovirus—more common in immunosuppressed patients (HIV positive or transplant recipients). Irreversible renal failure may ensue. • Polyomavirus (BK)—the renal transplant population are more spe- cifically at risk of BK virus inducing AIN and acute cellular rejec- tion. This polyomavirus is present in the urothelium of 60 to 80% of people, with immunosuppression allowing it to become a significant pathogen in the renal transplant, resulting in BK virus-associated nephropathy. Management generally involves reduction in immuno- suppression, with the use of ciprofloxacin, cidofovir, and leflunomide also advocated (but without convincing evidence of efficacy). • Toxoplasmosis—AIN is uncommon but can occur as part of sys- temic infection. • Leishmaniasis—disseminated leishmaniasis (kal-azar) can pre- sent with acute kidney injury from AIN. It tends to resolve. • Mycobacterium—these have been recognized as inducing AIN and, along with toxoplasmosis and leishmaniasis, are a commoner cause of AIN than drug-induced cases in developing countries. In septicaemia, bacteria such as Escherichia coli and staphylococci and fungal elements such as Candida albicans can directly invade the renal parenchyma and lead to the development of microabscesses, which are found on diagnostic renal biopsy. Immune • Systemic lupus erythematosus—lupus is associated with de- position of immunoglobulins and complement. Deposits may be extensive and widespread. Cellular infiltrates include mono- nuclear cells, but also on occasion neutrophils. Although the tubulointerstitial infiltrate usually coexists with significant glom- erulonephritis, it has been found in isolation. • Sjögren’s syndrome—may be associated with renal tubular acid- osis. IgG and C3 may be detected on immunofluorescent staining on the tubular basement membrane. • Sarcoidosis—can be coupled with the formation of typical granu- lomas in the interstitium. Associated hypercalcaemia and cellular infiltrate may lead

to dialysis-dependent renal failure. • IgG4 related kidney disease—lymphoplasmacytic cell-rich tubulointerstitial nephritis occurs with increased IgG4-positive plasma cells and storiform fibrosis. It can be associated with type 1 autoimmune pancreatitis, but is now considered to encompass various multiorgan inflammatory conditions. • Tubulointerstitial nephritis with uveitis (TINU) syndrome— described by Dobrin in 1975, uveitis may precede or follow the renal dysfunction. Autoimmune pathogenesis is suspected, with a strong association with specific HLAs (DQA1 *01/DQB1*05/ DRB1*01). This commonly affects pubertal females, responds to oral steroids, but is prone to relapse. • Antitubular basement membrane antibodies have been reported in rare idiopathic forms. • A variety of primary glomerulonephritides may cause a secondary tubulointerstitial inflammation and nephritis, for example, in the context of antiglomerular basement membrane antibodies and coexistent antitubular basement membrane antibodies (occurring in 50%), or membranous glomerulonephritis. Box 21.9.1.1 Main causes of acute interstitial nephritis Drugs • Proton pump inhibitors: — Esomeprazole — Omeprazole — Lansoprazole — Pantoprazole — Rabeprazole • Antibiotics: — Cephalosporin — Ciprofloxacin — Co-trimoxazole and other sulphonamides — Erythromycin — Methicillin — Other penicillin derivatives — Rifampicin — Vancomycin • Nonsteroidal anti-inflammatory drugs • Diuretics: — Furosemide (frusemide) — Thiazides — Triamterene • Chemotherapy agents: — Bacille Calmette–Guérin (BCG) — Ifosfamide — Tyrosine kinase inhibitors • Others: — Aciclovir — Allopurinol — Captopril — Clofibrate — Clozapine — Diphenylhydantoin — Etanercept — Fenofibrate — H2-receptor blockers — Indinavir — Interferon-α — Paracetamol — Phenindione — Phenobarbital — Phenothiazine — Salicylate derivatives — Streptokinase — Valproate — Warfarin Infectious • Bacterial: — Brucellosis — Legionella — Leptospirosis — Mycoplasma — Rickettsia — Streptococci, including pneumococci — Syphilis — Tuberculosis — Typhoid fever • Viral: — Polyomavirus (BK) — Coxsackie virus — Cytomegalovirus — Echovirus — Epstein–Barr virus — Hantavirus — HIV — Measles — Parvovirus B19 • Parasitic: — Leishmania — Toxoplasma Systemic diseases • Lupus erythematosus • Sarcoidosis • Sjögren’s syndrome Idiopathic • Associated with uni- or bilat- eral uveitis (TINU syndrome) • Isolated Adapted with permission from Droz D, Chauveau D (2003). Acute intersti- tial nephritis. In: Warrell DA, et al. (eds). Oxford Textbook of Medicine, p 35.

21.9.1 Acute interstitial nephritis 4953 Pathogenesis AIN is characterized by tubulitis with a heavy cellular infiltrate. Renal dendritic cells commence a process that results in intersti- tial fibroblastic cells expressing a variety of growth factors and cytokines such as transforming growth factor-β (TGF-β) and platelet-derived growth factor, which leads to inflammatory cas- cades and subsequent production of extracellular matrix proteins (collagens, fibronectin, laminin) and fibrotic change. This results in tubular destruction and the development of glomerular scler- osis. There are conflicting views on the role of fibroblasts derived from epithelial-to-mesenchymal transition having a vital im- portance in tubulointerstitial fibrosis development. This process progresses to the classic pathological changes of chronic intersti- tial nephritis. There are two possible mechanisms by which AIN develops: • Antigen-driven immunogenicity—AIN is classically associated with an infiltrate of T lymphocytes (both helper-inducer and suppressor-cytotoxic). This leads to T-cell-mediated hypersensi- tivity and cytotoxic T-cell injury. The presence of CD4 helper T cells at the site of injury indicates immune activation. Th1 helper cells (releasing TNFβ and γ-interferon) favour delayed-type hypersensitivity responses and the production of CD8 cytotoxic lymphocytes, and Th2 cells (releasing IL-5 and IL-4) attract eo- sinophils and help B cells form plasma cells that secrete antibodies. The presence of TGFβ1 acts as a proinflammatory molecule and is the most important

profibrotic factor. In proton pump inhibitor- induced AIN, CD4+ lymphocytic aggregates combined with costaining of CD4/IL-17A/F suggest a Th17-mediated inflamma- tory process. The presence of T-bet+ cell infiltrates point to add- itional Th1 involvement. • Humoral immunogenicity—although T cells are the main vil- lain implicated in pathogenesis, there is also evidence in ex- perimental animal models to implicate a role for the humoral immune system. This involves tubular basement membrane antibodies and complement. This process is active in the TINU syndrome, when there is an increase in IgG reactive against a 125-kDa kidney protein. The exact pathogenesis of drug-induced AIN is yet to be elu- cidated. It is thought that the drug or its metabolites act as either haptens (mimicking renal antigens) or deposit as circulating im- mune complexes. This is believed to stimulate a T-cell hypersensi- tivity reaction. Evidence for this theory is derived, in part, because of the extrarenal manifestation of hypersensitivity (rash, arthralgias, and eosinophilia). Pathology On light microscopy, the renal biopsy typically shows an infiltrate within the interstitium of T lymphocytes (especially CD4+ and CD8+ cells), monocytes, macrophages (expressing CD14+ and CD68+ in addition to cell activation markers), and possibly poly- clonal plasma cells and eosinophils (Fig. 21.9.1.1). The infiltrate may vary in intensity. There may be extensive interstitial oedema. If granulomas have formed, then the differential includes a drug reaction, sarcoidosis, tuberculosis, or acute bacterial infections (Fig. 21.9.1.2). Fibrosis within the interstitium has been detected within 2 weeks, as a component of the reparative process. The tubules themselves may show necrosis or signs of regeneration. In primary AIN, when the sample is examined by light mi- croscopy or immunofluorescent techniques, the glomeruli and vessels are either unremarkable or show only minor change. Immunofluorescence of the tubules and interstitium may stain positive for antitubular basement membrane antibodies, IgG and IgM in addition to fibrinogen. Linear IgG and C3 deposition is rarely found, although has been associated with antibiotic- induced disease (β-lactams and ciprofloxacin). Electron mi- croscopy reveals altered continuity of the tubular basement membrane. Fibrosis within the interstitium has been detected within 2 weeks as a component of the reparative process. Fig. 21.9.1.1 Renal biopsy (haematoxylin and eosin stain), demonstrating AIN with cellular infiltrate and sloughing of tubular epithelial cells. Fig. 21.9.1.2 Granuloma in AIN. Adapted with permission from Baker R. Acute tubulointerstitial nephritis: overview. In: Turner N, Lameire N, Goldsmith DJ, Winearls CG, et al. Oxford Textbook of Clinical Nephrology. 4th ed. Oxford: Oxford University Press (2015).

 Epidemiology AIN is not a common entity, being found in 1 to 3% of unselected renal biopsy series. Its exact incidence is difficult to gauge as renal physicians apply different criteria for performing diagnostic renal bi- opsies. However, most series suggest 15 to 27% of kidney biopsies per- formed for investigation of acute kidney injury demonstrate AIN, the higher percentage being reported where the cause of AKI is unknown and in the presence of inactive urinary sediment (i.e. lack of heavy proteinuria, lack of significant haematuria, or lack of presence of dys- morphic red blood cells). The prevalence of AIN may be increasing, especially in the elderly, possibly reflecting more diagnostic kidney biopsies or an increased incidence of drug-induced AIN. Clinical features The clinician should always consider AIN in any patient with unex- plained acute kidney injury, with or without specific tubular dysfunction. It is also important to consider AIN in a patient with chronic kidney dis- ease whose renal function suddenly deteriorates at a rapid rate. A thor- ough drug history is essential, including over-the-counter medications, herbal compounds, and other nonprescription agents, and the dates/ duration of exposure. Given that drug-induced AIN is an idiosyncratic reaction, it must be presumed that all

drugs might be causative. Drug-induced AIN may present with a classic allergic response, including fever, rash, arthralgias, and eosinophilia/eosinophiluria. The recognized clinical pattern of drug-induced AIN has changed since the disappearance of the classic methicillin-induced damage. These systemic features may present early (days to weeks after drug exposure), or up to a mean of 3 months following drugs such as the proton pump inhibitors. With drugs such as the NSAIDs, it can occur up to years later. In patients who are surreptitiously rechallenged with an offending drug, the onset of AIN is rapid. The development of AIN is not dose related (Table 21.9.1.1). Proton pump inhibitors Proton pump inhibitors are one of the most widely prescribed classes of drugs in the Western world. All five drugs in the class have been reported as causative agents. The triad of fever, rash, and eo- sinophilia associated with classical methicillin-induced AIN is less prominent or even absent in proton pump inhibitor-induced AIN. The presenting complaints are nonspecific in nature, including tiredness, nausea, and weight loss. The most common abnormalities on investigation, apart from raised serum creatinine, are low-level proteinuria, pyuria, and eosinophiluria. Due to the widespread availability of these drugs, both over the counter in some countries and on prescription, there is a high risk of inadvertent rechallenge unless patients are clearly counselled. This iatrogenic complication may be devastating, hence education of all prescribing doctors (including general practitioners, gastroenterol- ogists, and surgeons) in addition to pharmacists is warranted. NSAIDs This class of drugs (including selective COX-2 inhibitors) rarely causes extrarenal manifestation, but concurrent nephrotic syn- drome with heavy proteinuria and oedema is common, being present in up to 70% of cases. Macroscopic haematuria is rare. In Europe, fenoprofen accounts for up to 50% of cases. Precise history taking is imperative because these medications are readily available over the counter, are usually taken on an ‘as-needed’ basis, and many patients may not regard them as ‘drugs’ unless specifically asked about them by the clinician. β-Lactam antibiotics These agents cause the ‘classic’ allergic drug-induced AIN. Occurring within a few days or up to 2 months after starting treatment, fever, skin rash, arthralgias, eosinophilia, and renal impairment are evident. Other drugs of note The use of herbal medicines has increased in developed coun- tries: these are often incorrectly believed by patients to be in-nocuous, but they can cause AIN. Cocaine abuse can result in AIN, also in acute kidney injury from rhabdomyolysis and arterial hyper- tension induced by intense vasoconstriction. Deferasirox (oral iron chelator), pamidronate, amlodipine, and tyrosine kinase inhibitors (which more commonly produce nephrotic-range proteinuria and hypertension) can cause acute kidney injury due to AIN. Differential diagnosis The differential diagnosis includes other causes of renal impairment. The differentiation of acute tubular necrosis from AIN may be dif- ficult. In this situation, renal biopsy is required to conclusively con- firm or dismiss a provisional diagnosis. In contrast, glomerulonephritis generally presents with signifi- cant proteinuria (>1 g/day; urinary albumin:creatinine ratio (ACR)

> 60 mg/mmol; urinary protein:creatinine ratio (PCR) >100 mg/ mmol), in addition to dysmorphic red cells and granular/cellular casts on freshly spun urine microscopy. When assessing kidney biopsy specimens, the infiltrate of mono-nuclear cells needs to be differentiated from a monoclonal infiltrate, which would be found be in renal lymphoma or leukaemia. Table 21.9.1.1 Clinical features of AIN (data pooled from several studies). Acute kidney injury 100% Acute kidney injury requiring renal replacement therapy 40% Arthralgia 45% Rash 18% Fever 32% ‘Allergic triad’ (fever, rash, and arthralgia) 10% Eosinophilia 31%

> Nonvisible haematuria 67% Visible haematuria 5% Leucocyturia 82% Non-nephrotic-range proteinuria 93% Nephrotic-range proteinuria 2.5% Nephrotic syndrome 0.8% Proton pump inhibitors, NSAIDs, and β-lactam antibiotics are the most commonly found causes of iatrogenic AIN. Reproduced with permission from Baker R. Acute tubulointerstitial nephritis: overview. In: Turner N, Lameire N, Goldsmith DJ, Winearls CG, et al. Oxford Textbook of Clinical Nephrology. 4th ed. Oxford: Oxford University Press (2015). Copyright © 2015 Oxford University Press.

21.9.1 Acute interstitial nephritis 4955 Clinical investigation Laboratory testing demonstrates an elevated urea and creatinine. There may be associated biochemical changes reflecting tubular dysfunction such as hypo- or hyperkalaemia, aminoaciduria, glyco- suria, uricosuria, or alterations in serum bicarbonate. Either type I (distal) or type II (proximal) renal tubular acidosis patterns may predominate. The full blood count may reveal a high eosinophil count (up to 80% in drug-induced AIN caused by β-lactam antibiotics, but less commonly in other drug-induced causes). Microscopic examination of the urine may demonstrate eosino- phils when stained with Wright's or Hansel's stain. These stains are pH dependent. Other causes of eosinophils in the urine include prostatitis, bladder carcinoma, eosinophilic cystitis, and cholesterol emboli. Eosinophils in the urine have a sensitivity of 25 to 40%, a specificity of 72%, and a positive predictive value of 3 to 30%. The use of urine eosinophils as a screening test with such poor sensitivity and low positive predictive value is not recommended: it may not provide solid evidence and may delay renal biopsy and treatment. There may be nonspecific increases in inflammatory markers including erythrocyte sedimentation rate, C-reactive protein, and globulin concentrations. The urine typically has low-range proteinuria (<1 g/day; urinary ACR <60 mg/mmol; urinary PCR <100 mg/mmol). Urinary biomarkers of acute kidney injury such as monocyte chemoattractant protein-1 and neutrophil gelatinase-associated lipocalin have been compared against renal biopsy findings in AIN, but remain only an experimental tool. Gallium scans have been assessed as another diagnostic tool in helping to differentiate AIN from acute tubular necrosis. They are positive in AIN but negative in the latter. Kidneys with AIN en- hance as a result of the binding of gallium-67 to lactoferrin, which is produced, released, and found on the surface of lymphocytes within the interstitium. Although not giving a definitive diagnosis, it may be of assistance when renal biopsy is contraindicated or re- fused. Fluoro-2-deoxy-d-glucose positron emission tomography accumulates not only in cancer cells but also in the lymphocytes, macrophages, and neutrophils of inflammatory reactions, but fur- ther assessment is required to judge the utility of this imaging mo- dality in AIN. Renal biopsy is the gold standard when making the diagnosis of AIN. Its primary usefulness is to confirm or exclude a diagnosis. The clinician is often faced with a patient who presents with an elevated creatinine/reduced estimated glomerular filtration rate, inactive urine sediment, and a long list of possible offender medications that may cause AIN. This means that a strong argument can be made for performing a renal biopsy in all cases of suspected AIN, with the exception being where the clinician is reasonably confident of the diagnosis and judges that biopsy in the particular patient would con- stitute a greater risk than that of stopping any likely offending drug and giving steroids. Treatment The diagnosis of drug-induced AIN is vital as prompt identification and discontinuation of the causative agent facilitates recovery of renal function. Steroid treatment is problematic. Immediate verses delayed or no treatment with steroids may result in a lower subsequent creatinine level, with a correlation between the delay in steroid treatment and the final

serum creatinine, but there are no randomized controlled trials, only retrospective observational data. If steroids are prescribed, then a standard regimen would be oral prednisone at 1 mg/kg per day, tapered to zero over a 6- to 8- week period. Steroid resistance may require the addition of other immunosuppressants such as cyclophosphamide, ciclosporin, and mycophenolate. Plasma exchange has been utilized in patients testing positive for tubular basement membrane antibodies. Supportive treatment may be required if the degree of uraemia warrants, including renal replacement therapy with dialysis. Prognosis Significant recovery of renal function, with return of serum cre- atinine to baseline or near baseline, can be anticipated in most cases of AIN, but this does not happen in all cases, and some even pro- gress to endstage chronic kidney disease. The prognosis depends on the severity and degree of interstitial fibrosis. Other parameters that predict a less good outcome are high initial creatinine, renal impair- ment that has been present for more than 3 weeks, and granulomata or more pronounced interstitial cellular infiltrates on renal biopsy. The phenotype of inflammatory cells or the degree of tubulitis has not been shown to be prognostic. The pattern of recovery often follows two stages: a rapid improve- ment over 6 to 8 weeks and then a slower phase of improvement that may occur over the following 12 months. Likely developments in the near future Treatment of this condition has not been subject to the rigors of a randomized controlled trial, particularly looking at the benefits of corticosteroids. Due to the low incidence of this entity, a multicentre study would be required. This is unlikely to occur without a con- certed effort from a national clinical trials network. Future studies will be required to ascertain whether there are any epidemiological factors in patients that can predispose them to AIN. FURTHER READING Bagnis CI (2004). Herbs and the kidney. Kidney Int, 44, 1–11. Clarkson MR, et al. (2004). Acute interstitial nephritis: clinical features and response to corticosteroid therapy. Nephrol Dialysis Transplant, 19, 2778–83. Clive DM, Vanguri VK (2018). The syndrome of tubulointerstitial nephritis with uveitis (TINU). Am J Kidney Dis, 72, 118–28. Councilman WT (1893). Acute interstitial nephritis. J Exp Med, 3, 393–420. Dobrin RS, Vernier RL, Fish AL (1975). Acute eosinophilic inter- stitial nephritis and renal failure with bone marrow lymph node granulomas and anterior uveitis: a new syndrome. Am J Med, 59, 325–33. Geevasinga N, et al (2006). Proton pump inhibitors and acute intersti- tial nephritis. Clin Gastroenterol Hepatol, 4, 597–604.

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