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section 21 Disorders of the kidney and urinary tract 5012 Systemic sclerosis DeMarco PJ, et al. (2002). Predictors and outcome of scleroderma renal crisis: the high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial. Arthritis Rheum, 46, 2983–9. Denton C, et al. (2009). Renal complications and scleroderma renal crisis. Rheumatology (Oxford), 48, iii32–5. Kowal-Bielecka O, et al. (2009). EULAR recommendations for the treat- ment of systemic sclerosis: a report from the EULAR Scleroderma trials and research group (EUSTAR). Ann Rheum Dis, 68, 620–8. Nagaraja V (2019). Management of scleroderma renal crisis. Curr Opin Rheumatol, 31, 223–30. Penn H, et al. (2007). Scleroderma renal crisis: patient characteristics and long-term outcomes. Q J Med, 100, 485–94. Steen VD (1994). Renal involvement in systemic sclerosis. Clin Dermatol, 12, 253–8. Steen VD (2001). Treatment of systemic sclerosis. Am J Clin Dermatol, 2, 315–25. Teixeira L, et al. (2008). Mortality and risk factors of scleroderma renal crisis: a French retrospective study in 50 patients. Ann Rheum Dis, 67, 110–16. Rheumatoid arthritis Adu D, et al. (1993). Glomerulonephritis in rheumatoid arthritis. Br J Rheumatol, 32, 1008–11. Boers M (1990). Renal disorders in rheumatoid arthritis. Semin Arthritis Rheum, 20, 57–68. Esteve V, et al. (2006). Renal involvement in amyloidosis. Clinical out- comes, evolution and survival. Nefrologia, 26, 212–17. Hall CL, et al. (1987). The natural course of gold nephropathy: long term study of 21 patients. BMJ, 295, 745–84. Hall CL, et al. (1988). Natural course of penicillamine nephropathy: a long term study of 33 patients. BMJ, 296, 1085–6. Harper L, et al. (1997). Focal segmental necrotizing glomeruloneph- ritis in rheumatoid arthritis. QJM, 90, 125–32. Honkanen E, et al. (1987). Membranous glomerulonephritis in rheuma- toid arthritis not related to gold or D-penicillamine therapy: a report of four cases and review of the literature. Clin Nephrol, 27, 87–93. Kuznetsky KA, et al. (1986). Necrotizing glomerulonephritis in rheumatoid arthritis. Clin Nephrol, 26, 257–64. Stokes MB, et al. (2005). Development of glomerulonephritis during anti-TNF-alpha therapy for rheumatoid arthritis. Nephrol Dial Transplant, 20, 1400–6. Uda H, et al. (2006). Two distinct clinical courses of renal involvement in rheumatoid patients with AA amyloidosis. J Rheumatol, 33, 1482–7. Sjögren’s syndrome Goules A, et al. (2019). Renal involvement in primary Sjogren’s syn- drome: natural history and treatment outcome. Clin Exp Rheumatol, 37 Suppl 118(3), 123–32. Shioji R, et al. (1970). Sjogrens syndrome and renal tubular acidosis. Am J Med, 48, 456–63. Tu W, et al. (1968). Interstitial nephritis in Sjogren’s syndrome. Ann Intern Med, 69, 1163–70. Mixed connective tissue disease Kitridou R, et al. (1986). Renal involvement in mixed connective tissue disease: a longitudinal clinicopathologic study. Semin Arthritis Rheum, 16, 135–45. Sharp G, et al. (1972). Mixed connective tissue disease- an appar- ently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J Med, 52, 148–59. Drug nephrotoxicity Clive D, Stoff J (1984). Renal syndromes associated with anti- inflammatory drugs. N

Engl J Med, 310, 563–72. De Broe M, Elseviers M. (2009). Over the counter analgesic use. J Am Soc Nephrol, 20, 2098–103. Elseviers M, et al. (1995). High diagnostic performance of CT scan for analgesic nephropathy in patients with incipient to severe renal failure. Kidney Int, 48, 1316–23. Joint Formulary Committee. British national formulary (online). BMJ Group and Pharmaceutical Press, London. https://www. medicinescomplete.com/mc/bnf/current/ Pusey C, Saltissi D, Bloodworm L (1983). Drug associated acute inter- stitial nephritis: clinical and pathological features and the response to high dose steroid therapy. Q J Med, 52, 194–211. Sandler D, Burr F, Weinberg C (1991). Nonsteroidal anti- inflammatory drugs and risks for chronic renal disease. Ann Int Med, 115, 165–72. Savill J, Chia Y, Pusey C (1988). Minimal change nephropathy and pemphigus vulgaris associated with penicillamine treatment of rheumatoid arthritis. Clin Nephrol, 29, 267–70. 21.10.4 The kidney in sarcoidosis Ingeborg Hilderson and Jan Donck ESSENTIALS Sarcoidosis is associated with a broad spectrum of renal manifest- ations, but clinically important disease occurs in few patients. The most common cause of renal dysfunction is abnormal calcium me- tabolism: untreated chronic hypercalcaemia and hypercalciuria causes progressive tubulointerstitial inflammation with associated calcium deposits, leading to nephrocalcinosis, which is the leading cause of chronic kidney disease. Interstitial granulomatous nephritis is the most typical histological finding, but development of renal in- sufficiency is unusual. A range of glomerulopathies can be associated with sarcoidosis. When treatment is required, steroids are the first line, with various steroid-sparing agents used in cases that are refractory. Introduction Sarcoidosis is a multisystem inflammatory disease characterized by the presence of noncaseating epithelioid granulomas. These granulomas can resolve without sequelae or result in the devel- opment of fibrosis. The disease has a benign course with spontan- eous resolution in up to two-third of cases. However, in one-third a chronic disorder develops, leading to significant organ impair- ment. Sarcoidosis most frequently involves the lungs, but may af- fect any organ system. The most common sites of extrapulmonary disease include skin, eyes, liver, spleen, peripheral lymph nodes,

21.10.4 The kidney in sarcoidosis 5013 central nervous system, and heart. The incidence of renal in- volvement remains unclear. There is a great difference in reported prevalence due to the heterogeneity of renal manifestations and the often insidious nature of the disease.

Clinical presentations Sarcoidosis is associated with a broad spectrum of renal mani- festations, but clinically important disease occurs in only a few patients. The most prevalent cause of renal dysfunction is a dis- ordered calcium metabolism. Interstitial granulomatous neph- ritis is the most typical histological finding, but development of renal insufficiency is unusual. Finally, there is a wide range of glomerulopathies associated with sarcoidosis. Different types of renal sarcoidosis can coexist. Calcium metabolism Epidemiology Hypercalcaemia occurs in approximately 10 to 20% of patients with sarcoidosis and hypercalciuria is found in up to 50% of patients. Pathogenesis In sarcoidosis and other granulomatous diseases there is an in- creased activity of 1-α-hydroxylase, which is synthetized by granulomas and activated macrophages. This enzyme activity is re- sponsible for the increase in 1,25-dihydroxy vitamin D (calcitriol) and is resistant to negative feedback mechanisms. Calcitriol aug- ments the gastrointestinal calcium absorption, stimulates the osteoclast activity and bony reabsorption, and increases renal tubular calcium reabsorption. The net result is hypercalcaemia, which is known to cause renal dysfunction by several different mechanisms (Box 21.10.4.1). The rise in calcitriol suppresses the production of the parathy- roid hormone. Along with an increased renal calcium load, this results in hypercalciuria. Untreated, chronic hypercalcaemia and hypercalciuria causes a progressive tubulointerstitial inflamma- tion with associated calcium deposits, leading to nephrocalcinosis, which is the leading cause of chronic

kidney disease in sarcoidosis. Furthermore, hypercalciuria predisposes to nephrolithiasis and obstructive uropathy. Interstitial nephritis with granuloma formation Epidemiology Granulomatous interstitial nephritis is the most common renal le- sion seen on biopsy, but in only a few patients does this cause clin- ically significant disease. The true incidence is unknown, but in autopsy studies of patients with sarcoidosis, a granulomatous infil- trate is found in the kidneys in 7 to 23%. Clinical course Granulomatous interstitial nephritis is usually present when the initial diagnosis of systemic sarcoidosis is made and rarely de- velops in patients who have longstanding sarcoidosis. Most often there is diffuse active sarcoidosis, although isolated renal disease is an accepted entity. Interstitial nephritis has an insidious na- ture and is asymptomatic until late in the course of the disease when severe kidney dysfunction develops as a result of progres- sive fibrosis. It has a highly variable course with a tendency to wax and wane, either spontaneously or under treatment. Relapses are frequent. Diagnosis Screening for renal disease is important. Renal function tests, measurement of serum calcium, and urine analysis should be performed systematically both during initial evaluation and the follow-up of patients with sarcoidosis. Whenever granuloma- tous interstitial nephritis is suspected, a histopathological con- firmation should be attempted. Noncaseating granulomas are the hallmark of the disease, but they are nonspecific (Fig. 21.10.4.1). Box 21.10.4.1 Mechanisms of renal dysfunction caused by hypercalcaemia • Vasoconstriction of the afferent arteriole, causing a decrease in glom- erular filtration • Inhibition of Na+/K+-ATPase leading to urinary sodium wasting with polyuria and dehydration • Decreased sensitivity to antidiuretic hormone • Acute tubular necrosis (a) (b) (c) Fig. 21.10.4.1 Granulomatous interstitial nephritis. (a) On the left there is a localized inflammation of the renal parenchyma, which is not present on the right (haematoxylin and eosin stain, original magnification ×100). (b) Further magnification of the inflammation. There is a granulomatous infiltration with central collections of histiocytes surrounded by lymphocytes (haematoxylin and eosin stain, original magnification ×200). (c) Confirmation of the histiocytic character of the inflammation by an immunohistochemical staining with antibodies directed against CD68 (anti-CD68 stain, original magnification ×200). Courtesy of Prof. Dr. E. Lerut, University of Leuven, Belgium.

 Especially in case of isolated renal disease, other reasons of granu- lomatous infiltration should be excluded (Table 21.10.4.1). The absence of kidney biopsy findings does not exclude the diagnosis as renal sarcoidosis can be focal in nature and the typical lesions can easily be missed in biopsy. The urinary manifestations are also nonspecific: there is often mild proteinuria, or less frequently aseptic pyuria or nonvisible haematuria. In some cases, the urine sediment is bland. Glomerular disease Membranous nephropathy is the most common glomerular manifestation of sarcoidosis, although its incidence is very low. Some case reports suggest an association between sarcoidosis and focal segmental sclerosis, mesangioproliferative glomerulo- nephritis, IgA nephropathy, and crescentic glomerulonephritis, but a definitive causal relationship to these conditions has not been proven. Tubular dysfunction Tubular dysfunction is frequently associated with hypercalcaemia and granulomatous interstitial nephritis. It may present as isolated proximal or distal tubular acidosis, Fanconi’s syndrome, urinary concentration deficits, or metabolic alkalosis. Obstructive and vascular uropathy Obstructive uropathy usually results from nephrolithiasis, but in patients with sarcoidosis, obstruction may also be due to retroperi- toneal fibrosis or lymphadenopathy. Renal artery stenosis caused by granulomatous angiitis is an extremely rare complication of sarcoid- osis, often accompanied by arterial hypertension. Treatment Treatment is always required for renal disease, as it is for cardiac, ocular, and neurological manifestations of sarcoidosis, given the

substantial risk of end-organ damage. However, there is no standard of care and little is known about the optimal dose and duration of treatment. Hypercalcaemia and hypercalciuria Glucocorticoids are the mainstay of treatment (Table 21.10.4.2) as they block the 1-α-hydroxylase activity and diminish the in- testinal calcium absorption and bony resorption. Most often, a starting dose of prednisolone of 0.3 to 0.5 mg/kg once daily is re- commended, followed by a taper to a maintenance dose of 5–10 mg once daily. The total duration of treatment should be at least 12 months. Chloroquine is an alternative treatment. The optimal dose is unknown, but a daily dosage of 250 to 500 mg is most often used. Retinal toxicity is the major concern. Hydroxychloroquine (recommended daily dosing is 200–400 mg) is slightly less ef- fective, but carries a lesser risk of retinopathy. Ketoconazole in a daily dose of 600–800 mg can also be used. Hepatic toxicity is the major limiting side effect. The effect of these alternative forms of treatment is less predictable and slower than treatment with corticoids. Preventive measures such as ensuring adequate oral hydration, a low dietary intake of calcium, vitamin D, and oxalate, as well as the limitation of sunlight exposure play additional supportive roles. Thiazide use should be avoided given the substantial risk of aggra- vating hypercalcaemia. Interstitial nephritis with granuloma formation Glucocorticoids Glucocorticoids are the cornerstone of treatment (Table 21.10.4.3). Most authors recommend a starting dose of 0.5 to 1 mg per kg pred- nisone once daily, depending on the severity of the disease. The ini- tial dose should be maintained for 4 weeks to allow improvement and/or stabilization of renal function. Most patients respond rapidly to treatment but a full recovery of renal function is rare. Patients with a poor response after 1 month tend to have a worse renal out- come and are more susceptible to relapse. After 4 weeks of treat- ment, the dose can be tapered by 5 mg each week until a daily dose of 5 to 10 mg is reached. There is an increased risk of relapse if corticosteroids are tapered too quickly. In this eventuality, the dose should be augmented to the last dose that was effective, with an increase to the initial dose if there is no improvement after 4 weeks. Subsequent tapering should be more gradual. However, in some patients it is impos- sible to taper the glucocorticoids adequately. Given the many side effects of a prolonged treatment with high-dose glucocorticoids, Table 21.10.4.1 Differential diagnosis of granulomatous nephritis Diagnosis Example Drug reaction β-lactam antibiotics, nonsteroidal
anti-inflammatory drugs Infections Tuberculosis, chronic fungal infection Autoimmune disorders Sarcoidosis, granulomatosis with polyangiitis Neoplasia Lymphoma Foreign body reaction Heroin Table 21.10.4.2 Treatment of hypercalcaemia and hypercalciuria in sarcoidosis Standard of care: glucocorticoids Starting dose: 0.3–0.5 mg/kg per day Maintenance dose: 5–10 mg/day Total duration of treatment: at least 12 months Alternatives Chloroquine Dose: 250–500 mg/day Hydroxychloroquine Dose: 200–400 mg/day Ketoconazole Dose: 600–800 mg/day Preventive measures Limit sunlight exposure Low dietary intake of calcium, vitamin D, and oxalate Adequate oral hydration Avoid thiazide use

 a steroid-sparing agent (azathioprine or mycophenolate mofetil) can be added, with the intention of subsequently reducing the glucocorticoid dose. The ideal duration of maintenance therapy is unknown. A total duration of treatment of 18 to 24 months seems necessary to be ef- fective and to prevent relapse. For the few patients who suffer fre- quent relapses, lifelong treatment with low-dose glucocorticoids may be required. There are, however, important side effects from long-term steroid use which need to be balanced against the risk of progression to endstage renal disease. Azathioprine and mycophenolate mofetil Azathioprine and mycophenolate mofetil can be used as steroid- sparing agents or in patients with failure of or a strong contraindi- cation to continued corticosteroids. Treatment with these drugs

should only be started after at least 1 month of treatment with cor- ticosteroids, since this duration is needed to allow improvement or stabilization of renal function. The daily dose of azathioprine is 2 mg per kg, mycophenolate mofetil is dosed at 1 g, twice a day. However, it should be pointed out that the evidence in support of these second- line agents is very limited. Tumour necrosis factor-α inhibitors Tumour necrosis factor (TNF) is thought to be a major player in sar- coidosis through its role in the maintenance of granuloma forma- tion. TNFα inhibitors have therefore been suggested as appropriate treatment in cases of steroid-resistant sarcoidosis. They should only be used when at least one other immunosuppressive agent has been tried, or in patients who have developed severe steroid toxicity. Evidence is scarce. Infliximab is usually given in a dosage of 3 to 5 mg per kg at weeks 0, 2, and 6, followed by 3 to 5 mg per kg every 6 to 8 weeks thereafter. Adalimumab could be an interesting option for patients intolerant of infliximab, but more research is needed before its use can be advocated. Etanercept seems to have no bene- ficial effect in patients with sarcoidosis, as in other granulomatous diseases. Kidney transplantation Endstage renal disease secondary to sarcoidosis is very uncommon. One concluded that renal transplantation can be carried out safely with excellent graft and patient survival, although there was a rela- tively high rate of renal recurrence (17%). A short delay between the last episode of sarcoidosis and renal transplantation was a risk factor for recurrence. Experimental therapy With recognition of the role of cytokines in the pathogenesis of sar- coidosis, other immunosuppressive drugs including thalidomide, pentoxifylline, and rituximab have been proposed as steroid-sparing agents, but more data are needed before their use can be advocated. Conclusion Sarcoidosis may affect any organ, including the kidney. Disordered calcium metabolism is the most common cause of renal failure. Granulomatous interstitial nephritis is the most typical histological finding, but development of renal insufficiency is rare. The lack of large, randomized controlled treatment trials limits therapeutic options. Corticosteroids remain the cornerstone of treatment. The role of corticosteroid-sparing medications continues to evolve. FURTHER READING Berliner AR, Haas M, Choi MJ (2006). Sarcoidosis: the nephrologist's perspective. Am J Kidney Dis, 48, 856–70. Hilderson I, et al. (2014). Treatment of renal sarcoidosis: is there a guideline? Overview of the different treatment options. Nephrol Dial Transplant, 29, 1841–7. Mahévas M, et al. (2009). Renal sarcoidosis: clinical, laboratory, and histologic presentation and outcome in 47 patients. Medicine (Baltimore), 88, 98–106. Rajakariar R, et al. (2006). Sarcoid tubulo-interstitial nephritis: long- term outcome and response to corticosteroid therapy. Kidney Int, 70, 165–9. Table 21.10.4.3 Treatment of granulomatous interstitial nephritis in sarcoidosis Step 1: glucocorticoids Starting dose: • Major organ impairment: — Oral prednisone 1 mg/kg per day Or — Intravenous pulse methylprednisolone (3 days), followed by oral
prednisone 1 mg/kg per day • Milder disease: oral prednisone 0.5 mg/kg per day Keep initial dose for 4 weeks, if renal function does not stabilize/improve continue to step 2 After 4 weeks of treatment, reduce dose by 5 mg a week Maintenance dose: 5–10 mg daily Relapse: • Augment prednisone to the last dose that was effective and continue for 4 weeks • No improvement after 4 weeks: augment corticoids to the starting dose and continue for 4 weeks • Subsequent tapering: more gradual Total duration of treatment: 18–24 months Step 2: add another immunosuppressive agent Failure of corticosteroids Relative contraindication to corticosteroids Impossibility to taper the corticosteroids Azathioprine Dose: 2 mg/kg per day Mycophenolate mofetil Dose: 1 g, twice a day Subsequently reduce the corticosteroids by 5 mg a week until a daily dose of 5–10 mg is reached Step 3: add a TNFα inhibitor—infliximab Steroid-resistant sarcoidosis when at least one other immunosuppressive agent has been tried Severe steroid toxicity Dose: 2–5 mg/kg at weeks 0, 2, and 6 and every 6 to 8 weeks thereafter Experimental therapy Thalidomide, pentoxifylline, rituximab, etc.

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