Infections and the Kidney

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Clinical Scenario 1

A 71-year old woman with end-stage kidney disease (ESKD) secondary to diabetic nephropathy, maintained on twice-weekly haemodialysis (HD), was admitted for management of profuse rectal bleeding secondary to diverticulitis. She was catheterised and transfused with a unit of packed red cells. A week into her admission, she started vomiting and became listless. Her temperature and vital signs were normal. Urinalysis revealed a positive leukocyte esterase, and her urine bag and tubing acquired a purple colour (Fig. 14.1a). Urine samples obtained from the urine bag and urethral catheter did not have the purple coloration (Fig. 14.1b and c). The urethral catheter was removed and her urine cultured, yielding. *Escherichia coli* sensitive to Ceftazidime. She was treated with intravenous ceftazidime, with resolution of her symptoms, and a negative urine culture thereafter.

Clinical Scenario 2

An 11-year-old female, presented to the emergency department (ED) with a 2-week history of fever. For the previous 6 days, she had noted that her urine had become brown (sometimes referred to as "coke-coloured") followed by a reduced urine output, and generalized body swelling. Two days before admission she had become short of breath, and a few hours before she attended the ED she had suffered a seizure. She had had a skin infection 3 weeks prior to her symptoms. On examination, she was pale, febrile, in respiratory distress, with an impaired state of consciousness, with a Glasgow coma score of 8/15. Her temperature was 37.8 °C, her respiratory rate 38 breaths/min, BP 160/110 mmHg, and pulse 110/min. She had significant bilateral pitting leg oedema. It was also noted that she had multiple bilateral hyperpigmented macular skin lesions. She had demonstrable ascites and fine bilateral crepitations. Catheterization revealed the brown urine, with a urine flow rate of 0.3 mL/kg/h. Urinalysis showed blood, protein, leukocytes, and microscopy revealed red cell casts. Blood results: Sodium: 122 mmol/L, potassium: 5.6 mmol/L, HCO_3 12.4 mmol/L, chloride: 84.4, iCa: 1.01, BUN: 63.3 mmol/L, creatinine: 884 μmol/L, hae-

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D. Banerjee et al. (eds.), *Management of Kidney Diseases*,
https://doi.org/10.1007/978-3-031-09131-5_14

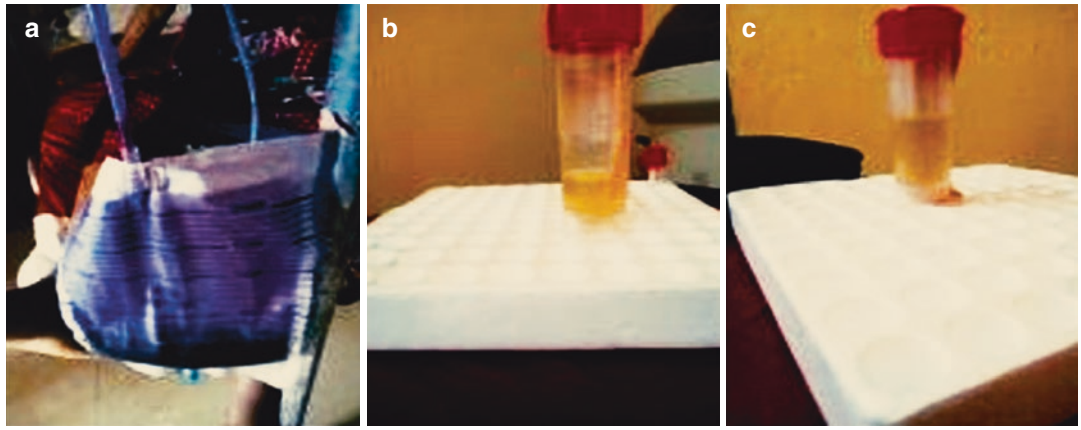

Fig. 14.1 The purple urine Bag Syndrome (PUBS) (**a**) shows purple discoloration of urine in the patient's catheter bag; (**b**) shows a catheter urine sample; (**c**) shows a urine bag sample. The purple urine bag syndrome occurs when colonic bacteria degrade tryptophan to indole. Indole is converted to indole sulphate in the portal circulation and once filtered into the urine is catabolized by indole sulphatase and bacteria to indigo and indirubin. Both pigments attach to the urine bag to stain it purple, though the urine retains its usual amber yellow colour [1]

moglobin: 8.3 g/dL, leukocytosis with neutrophila of 78%; ESR: 125 mm/h and qualitative ASO titre: elevated/positive, C3: not available. Ultrasonography: kidneys measured 11 × 4 cm and 10.8 × 3.6 cm, with increased echogenicity and moderate obliteration of sinoparenchymal differentiation.

A diagnosis of acute kidney injury (AKI) with hypertensive/uraemic encephalopathy secondary to post-streptococcal glomerulonephritis (PSGN) was made.

She had 3 sessions of haemodialysis, IV furosemide, fluid restriction, amlodipine, IV Sultamicillin tosylate initially and later, oral amoxicillin/clavulanate potassium.

The patient was followed-up for 4 months; her kidney function improved to an eGFR of 96 mL/min/1.73 m^2, although she continues to have dipstick haematuria.

Introduction

Infections cause kidney disease via diverse mechanisms, including by (1) direct tissue invasion; (2) indirectly by immune-mediated mechanisms which lead to glomerulonephritis; (3) acute kidney injury (AKI); (4) less common is nephrotoxic damage which occurs with medications and diagnostic procedures as part of patient management. The manifestations of disease depend on the patient's health status/immune defense mechanisms, the micro-organism, and numerous genetic and environmental factors. The different microorganisms that will be discussed in this chapter are listed below:

Bacteria

1. *Direct Injury To The Kidney*
   - Urinary tract infections
   - Reflux nephropathy
   - Mycobacteria
     - Tuberculosis
     - Leprosy
   - Leptospirosis

2. *Indirect or Immune-mediated Damage to the Kidney*
   - Bacterial Infection-Related Glomerulonephritis
   - Post-Streptococcal GN (PSGN)

3. *Kidney Injury as part of Ongoing Sepsis*
4. *Nephrotoxic Damage from Medications*

Viruses

- Dengue
- Hantavirus
- Ebola
- Parvovirus

- Polyoma virus
- Cytomegalovirus CMV
- Varicella
- Hepatitis viruses: HEV, HAV, HBV, HCV
- Human immunodeficiency virus HIV
- Severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2]

Protozoa and Parasites

- Malaria
- Schistosomiasis

Fungi

Bacterial Infections and Kidney Disease

A large number of bacterial infections cause kidney disease, via the mechanisms mentioned above; they include Gram-positive and negative cocci, Gram-positive and negative bacilli and coccobacilli, some not readily Gram-stained organisms such as *Mycobacterium* species and others like *Mycoplasma pneumonia* and *Chlamydia pneumonia.*

Mechanisms of Bacterial Infection-Related Kidney Diseases

Direct Injury to the Kidney

Urinary Tract Infections (UTIs)

Urinary tract infections (UTIs) are very common and caused mainly by gram negative bacteria. They affect >150 million people each year worldwide; 40–50% of women and 5% of men will invariably have an episode of UTI at least once in their life [2]. The incidence is highest in adolescent and childbearing females, peaking during the years of maximum sexual activity (18–39 years) [3]; this age-group is 30 times more likely to have UTI than their male counterparts [4]. However, the incidence of UTI increases in men >60 years, mainly because of prostatic obstruction, and approaches the incidence of UTI in women.

Epidemiology: Though community-acquired uncomplicated UTIs account for most infections, the prevalence of healthcare-acquired UTIs ranges from 12.9% in the US and 19.6% in Europe to 24% in developing countries [5]. Predisposing factors such as age, health status, catheterization and immunosuppression determine the dynamics of the infection. For example, whereas non-catheterized persons are more likely to suffer UTIs caused by a single bacterial species, catheterization/structural abnormalities predispose to UTIs caused by multiple bacterial species. In Clinical Scenario 1, the patient had 4 risk factors for UTI: age, female gender, immunosuppression (immune paresis related to her diabetes mellitus and uraemia), and catheterization [1].

Bacteria ascend through the urethra to the bladder, initiating symptomatic or asymptomatic bacteriuria, and subsequently reach the kidneys to cause pyelonephritis (ascending infection). Less commonly, infection can arise from haematogenous spread (descending infection).

UTIs are classified using several criteria: They are categorized using complication status, as listed below and in Tables 14.1, 14.2, 14.3, 14.5, where management is outlined for each category.

Table 14.1 Diagnosis & management of asymptomatic bacteriuria and uncomplicated UTIs

Category	Asymptomatic bacteriuria	Uncomplicated acute cystitis	Uncomplicated acute pyelonephritis
Investigations	**Urinalysis:** dipstick **MSU MC&S** **Diagnosis:** Presence of significant bacteriuria (Colony count of $>10^5$ CFU/mL) without symptoms [6, 7]	**Urinalysis:** dipstick bacteriuria/pyuria **MSU MC&S** **Microscopic urinalysis:** pyuria, bacteriuria, haematuria. **Bacteria:** *E. coli* (75–80%); Others: *K. pneumonia, S. saprophyticus, Enterococcus faecalis* **Definitive Diagnosis:** Colony count $>10^3$ CFU/mL	**Urinalysis:** dipstick bacteriuria or pyuria **MSU MC&S** **Microscopic urinalysis:** pyuria, bacteriuria, haematuria **Bacteria:** *E. coli* (75–80%); Others: *K. pneumonia, S. saprophyticus, Enterococcus faecalis* Send urine sample for culture and susceptibility testing **Definitive diagnosis**: Colony count of $>10^5$ CFU/mL [8]

(continued)

Table 14.1 (continued)

Category	Asymptomatic bacteriuria	Uncomplicated acute cystitis	Uncomplicated acute pyelonephritis
Treatment and Follow-up	Antibiotic therapy reserved for special cases: Pregnant women & those who have had urological procedures (NICE [6] and EAU [7] Guidelines on asymptomatic bacteriuria)	Based on NICE Guidelines on cystitis [9] (Fig. 14.2 shows an algorithm for management approach) [8] **Non pregnant women:** *First-choice agents (3-day course):* Nitrofurantoin (if eGFR ≥45 mL/min) 100 mg modified-release twice a day (or if unavailable, 50 mg four times a day) for 3 days; TMP 200 mg twice a day for 3 days *Second-choice agents:* Pivmecillinam hydrochloride 400 mg initial dose, then 200 mg three times a day for a total of 3 days or Fosfomycin 3 g single dose sachet **Pregnant women:** *First-choice agents (3-day course):* Nitrofurantoin (if eGFR ≥45 mL/min) 100 mg modified-release twice a day (or if unavailable, 50 mg four times a day) for 7 days *Second-choice agents:* Amoxicillin (only if MC&S results available and susceptible) 500 mg three times a day for 7 days Cefalexin 500 mg twice a day for 7 days Alternative second choices—Consult local microbiologist, choose antibiotics based on culture and susceptibility results **Men:** TMP: 200 mg twice a day for 7 days; Nitrofurantoin (if eGFR ≥45 mL/min) 100 mg modified release twice a day (or if unavailable, 50 mg four times a day) for 7 days. Use Beta-lactam antibiotics when recommended medications are inappropriate **Note:** Select antibiotics using local resistance patterns (antibiogram). TMP- SMX should be avoided if resistance ≥20% Follow-up visit with MSU is recommended for pregnant women, older females and all male patients. Further evaluation with ultrasound, CT-scan or cystoscopy is unnecessary in patients who respond well	Based on NICE Guidelines on acute pyelonephritis [6] **Non-pregnant women and men aged > 16 years:** *First choice oral antibiotics:* Cefalexin: 500 mg twice or three times a day (up to 1–1.5 g three or four times a day for severe infections) for 7–10 days Amoxicillin/Clavulanic acid 500/125 mg three times a day for 7–10 days or TMP 200 mg twice a day for 14 days (only if culture results are available and organisms are susceptible) ***First choice intravenous antibiotics*** *(if vomiting or unable to take orally or severely unwell). Antibiotics may be combined if susceptibility or sepsis is a concern. Review intravenous medications by 48 h and consider changing to oral antibiotics to complete duration of 7–10 days* Amoxicillin/Clavulanic acid (only in combination or if culture results are available and susceptible): 1.2 g three times a day; Cefuroxime: 750 mg to 1.5 g three or four times a day; Ceftriaxone: 1–2 g once a day; Ciprofloxacin: 400 mg twice or three times a day Gentamicin: Initially 5 mg/kg to 7 mg/kg once a day, subsequent doses adjusted according to serum gentamicin concentration; Amikacin: Initially 15 mg/kg once a day (maximum per dose 1.5 g once a day), subsequent doses adjusted according to serum amikacin concentration (maximum 15 g per course) *Second choice intravenous antibiotics*—consult local microbiologist **Pregnant women:** *First choice oral antibiotic:* Cefalexin: 500 mg twice or three times a day (up to 1 to 1.5 g three or four times a day for severe infections) for 7–10 days First choice intravenous antibiotic (if vomiting, unable to take oral antibiotics, or severely unwell) *Review intravenous medications by 48 h and consider changing to oral antibiotics to complete duration of 7–10 days* Cefuroxime: 750 mg to 1.5 g three or four times a day **For second choice antibiotics or combining antibiotics** if susceptibility or sepsis a concern: Consult local microbiologist

CT computerized tomography, *IV* intravenous, *IVU* intra-venous urogram, *MSU* mid stream urine microscopy, *MC&S* microscopy, culture and sensitivities, *TMP* trimethoprim, *TMP-SMX* trimethoprim-sulfamethoxazole

Table 14.2 Diagnosis & management of complicated UTIs, recurrent UTIs and urosepsis

Category	Complicated UTI	Recurrent UTIs: relapse/reinfection	Sepsis/urosepsis
Investigations	**Urinalysis**: Dipstick **MSU MC&S** Significant bacteriuria colony counts: Females: $>10^5$ CFU/mL Males: $>10^4$ CFU/mL Catheter samples: $>10^3$ CFU/mL [7] **Bacteria:** mainly *E. coli* Common others: *Proteus* species, *Klebsiella* species, *Pseudomonas* species Less commonly: *Serratia* species, *Enterococci*, *Staphylococci* **Imaging studies:** IVU, Imaging studies, such as sonography and CT-scan	**Urinalysis:** Dipstick **MSU MC&S** Colony count of 10^2 CFU/mL is diagnostic [9] **Imaging studies:** IVU, sonography and CT-scan	EAU Guidelines 2019 [7]: **Diagnosis of Sepsis**: Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more **or** quick SOFA (q SOFA) score: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mmHg or less. **Septic shock:** can be clinically identified by the need for a vasopressor to maintain a mean arterial pressure ≥65 mmHg and serum lactate level greater than 2 mmol/L (>18 mg/dL) in absence of hypovolemia Microbiology sampling on urine, two sets of blood cultures and if appropriate, drainage fluids **Imaging studies:** e.g. sonography and CT-scan should be done early

(continued)

Table 14.2 (continued)

Category	Complicated UTI	Recurrent UTIs: relapse/reinfection	Sepsis/urosepsis
Treatment and Follow-up	**EAU Guidelines 2019** [7]: Patients with systemic symptoms requiring hospital admission should be initially treated with an IV antimicrobial regimen: aminoglycoside with/without amoxicillin, or a second or third generation cephalosporin, or an *Extended-spectrum beta-lactamase* with or without an aminoglycoside Choice should be based on local resistance data and susceptibility results. Considering current resistance percentages of amoxicillin, co-amoxicillin/clavulanic acid, TMP and TMP-SMX, they should not be used for treatment of all complicated UTIs **NICE Guidance: 2018 Update** [10] Ceftolozane/tazobactam 1 g/0.5 g IV 8 hourly (very expensive compared to other antibiotics); Levofloxacin 500 mg (up to 750 mg IV daily); Piperacillin/tazobactam 4 g/0.5 g IV 8 hourly; Cefotaxime 2–12 g IV daily in divided doses; Cefuroxime 1.5 g IV 8 hourly; Ceftazidime 1–2 g IV 8 or 12 hourly; Ceftriaxone 1–2 g IV daily; Ciprofloxacin IV 400 mg 8 or 12 hourly or oral 500 mg 12 hourly; Meropenem 0.5–1 g IV 8 hourly; Gentamicin IV 3–6 mg/kg in divided doses or 160 mg once daily Duration of treatment: 10–14 days; closely related to the treatment of the underlying abnormality Follow-up urine cultures should be performed post treatment	Figure 14.3 shows an algorithm for management approach.) [12] for management Antibiotic prophylaxis [13]: Choose antibiotics depending on recent culture and susceptibility results. Select a different antibiotic for prophylaxis if treating an acute UTI **First choice:** TMP 200 mg single dose when exposed to a trigger, **or** 100 mg at night Nitrofurantoin (if eGFR ≥45 mL/min) 100 mg single dose when exposed to a trigger, **or** 50–100 mg at night **Second choice:** Cefalexin 500 mg single dose when exposed to a trigger, **or** 125 mg at night For those who have urological anomaly, correct surgically if possible **Correctable abnormalities** include: Infected stones, chronic bacterial prostatitis Infected atrophic kidneys, ectopic/duplex ureters Foreign bodies, etc.	**EAU Guidelines 2019** [7]: Commence intravenous antibiotics promptly to eliminate the infection Supportive care: Institute measures to prevent further injury (avoid nephrotoxic agents) Stabilize and maintain effective intravascular volume and renal perfusion Adopt early goal-directed therapy using volume and vasopressor support (fluid, vasopressors, blood products, and inotropes) to achieve and maintain a mean arterial pressure of 65 mmHg and a central venous pressure of 8–12 mmHg **Antibiotics for 7–10 days or longer:** Cefotaxime 2 g 8 hourly; Ceftazidime 1–2 g 8 hourly; Ceftriaxone 1–2 g daily; Cefepime 2 g 12 hourly; Piperacillin/tazobactam 4.5 g 8 hourly; Ceftolozane/tazobactam 1.5 g 8 hourly Ceftazidime/avibactam 2.5 g 8 hourly/5 mg/kg daily; Ertapenem 1 g daily; Imipenem/cilastatin 0.5 g 8 hourly; Meropenem 1 g 8 hourly

CT computerized tomography, *IV* intravenous, *IVU* intra-venous urogram, *MSU* mid stream urine microscopy, *MC&S* microscopy, culture and sensitivities, *TMP* trimethoprim, *TMP-SMX* trimethoprim-sulfamethoxazole

Table 14.3 Investigations and management of chronic tubulo-interstitial nephritis (TIN), genitourinary TB and leptospirosis

Category	Chronic TIN/chronic kidney disease (CKD)	Genitourinary TB	Leptospirosis
Investigations	Urinalysis: microscopy and dipsticks MSU MC&S Blood culture Imaging studies	Diagnosis of UGTB requires high index of suspicion. Patients who have insidious onset, non-specific symptoms with culture-negative pyuria in endemic regions must be evaluated for UGTB. Imaging studies (abdominal x-ray, MRI) may help diagnosis Confirm diagnosis with urine: at least 6 (preferably >9) specimens of urine, prostatic secretion or ejaculate cultured in Lowenstein–Jensen, Finn–II, and Middlebrook 7H9-12 media [13]. Detection of AAFB from samples by microscopy using Ziehl-Nielsen acid fast stain is unreliable, as M. smegmatis are acid-fast too [14] Histopathological examination is the gold standard, PCR has sensitivity and specificity of 87.5% and 86.7% respectively [13]. GeneXpert MTB/RIF outperforms AFB smear and culture for the detection of mycobacterium in urine samples [15]. Ultrasound-guided fine needle aspiration of the abscess/masses may show histologic evidence of UGTB. Other investigations: tuberculin provocation test with 20, 50 or 100 units injected subcutaneously; cystoscopy and ureteroscopy; bladder biopsy	Based on clinical and epidemiologic data and confirmed through Microscopic Agglutination Test (MAT) for serology identification and PCR amplification of DNA of the spirochete from blood [16]. However, MAT is most widely performed using 2 blood samples collected 2 weeks apart

(continued)

Table 14.3 (continued)

Category	Chronic TIN/chronic kidney disease (CKD)	Genitourinary TB	Leptospirosis
Treatment and Follow-up	Treat existing infection; Prevent future infections; Preserve renal function Institute conservative CKD management: Restrict dietary protein intake Aggressive BP control using antihypertensives like ACEi Commence kidney replacement therapy at end-stage	EAU Guidelines for UGTB [14] *First 2 months:* Isoniazid (INH) 300 mg daily; Rifampicin 600 mg daily; Ethambutol 1200 mg daily; Pyrazinamide 2000 mg daily; Pyridoxine 20 mg daily or 50 mg alt daily *Continuation phase (4 months):* Isoniazid (INH) 300 mg daily; Rifampicin 600 mg daily; Pyridoxine 20 mg daily or 50 mg alt daily *Dosage Calculation:* [14] *Anti-TB drug—dose mg/kg (body weight–daily dose)* *Isoniazid—5 mg/kg (300 mg)* *Rifampicin—10 mg/kg (<50 kg–450 mg; >50 kg–600 mg)* *Pyrazinamide—25–35 (<50 kg–1.5 g; >50 kg–2.0 g; >75 kg–2.5 g)* *Streptomycin—15–20 (<50 kg–0.75 g; >50 kg−1.0 g)* *Ethambutol—25 (2.0 g; 0.8–2.0 g)* *Ethionamide—5–15 (0.5–1.0 g)* Surgery includes: Abscess drainage, total or partial nephrectomy, epididymectomy, correction of ureteral strictures, etc.	Appropriate antibiotics such as penicillin or tetracycline are effective for leptospiral nephropathy [17]

AAFB alcohol & acid-fast bacilli, *ACEi* angiotensin converting enzyme inhibitors, *BP* blood pressure, *CKD* chronic kidney diease, *DNA* deoxy-ribonucleic acid, *EAU* European Association of Urology, *INH* isoniazid, *MAT* microscopic agglutination test, *MC&S* microscopy culture & sensitivities, *MSU* mid-stream urine, *PCR* polymerase-chain reaction, *TB* tuberculosis, *TIN* tubule-interstitial nephritis, *UGTB* uro-genital tuberculosis

Asymptomatic bacteriuria: Is defined as significant bacteriuria in a midstream urine (MSU) specimen in people with no relevant genitourinary symptoms, with uro-pathogens $>10^5$ CFU/mL in two consecutive samples in females, or a single sample in males [6, 7].

Uncomplicated UTIs: Consist of community-acquired cystitis (lower urinary tract infection with symptoms of dysuria, frequent and urgent urination and suprapubic pain) and pyelonephritis (infection of the renal parenchyma and pelvi-calyceal system with symptoms of fever and flank pain). Figure 14.2 and Table 14.1 outline an algorithm for management of uncomplicated UTIs [9].

Complicated UTIs: Infection associated with a structural/functional genitourinary tract anomaly or underlying diseases that increase risk of worse outcome [8]; such as: indwelling urinary catheters, urinary obstruction, anatomical abnor-

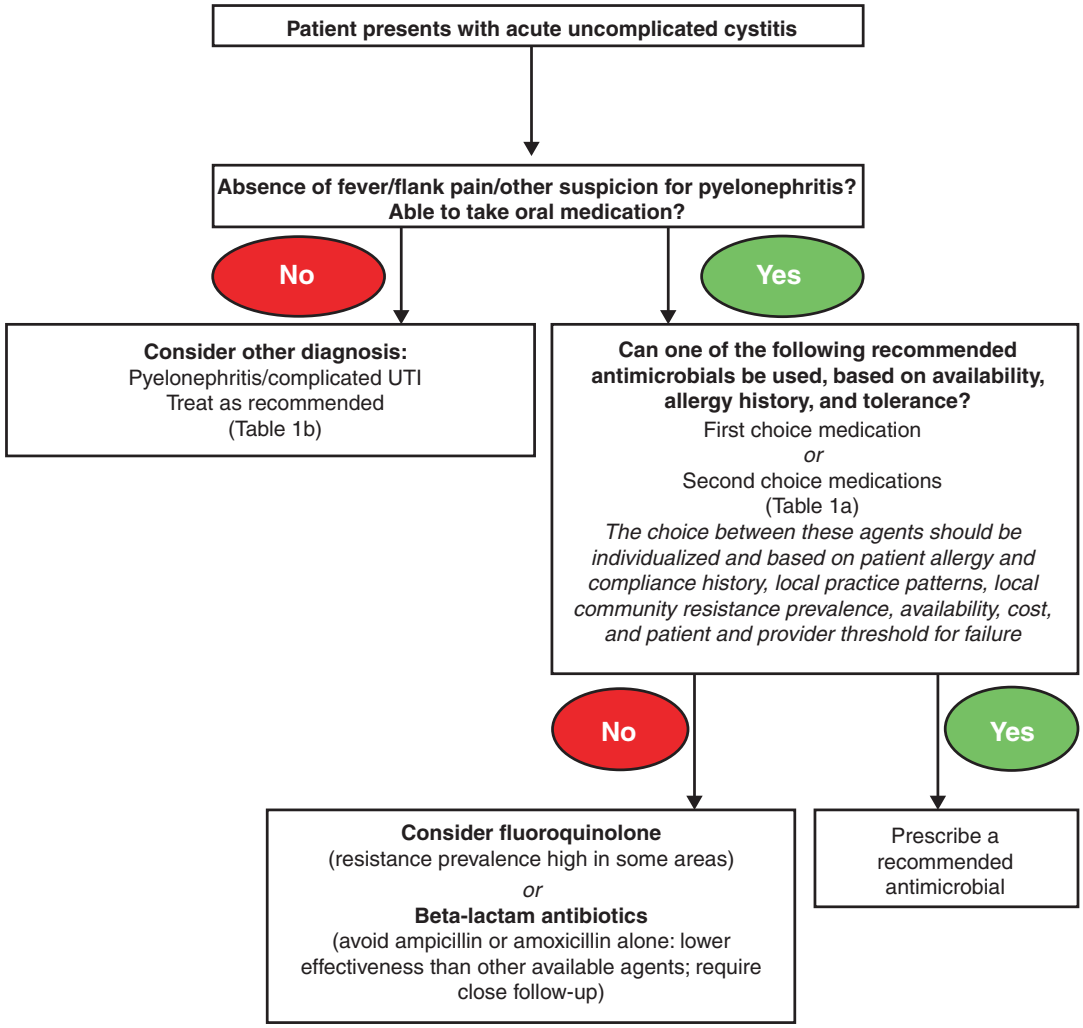

Fig. 14.2 Algorithm for the approach to management of acute uncomplicated cystitis (adapted from IDSA Guidelines [9]). *UTI* urinary tract infection

malities, peri-operative urinary tract infections, including kidney transplantation (Table 14.2).

Recurrent UTIs: Defined as at least three episodes of uncomplicated infection confirmed by urine culture over a 12-month period or 2 episodes over 6 months. They include lower and upper UTIs. The two types of recurrent UTI are:

Relapse—defined as recurrent UTI involving the same organism(s) after adequate therapy; and

Reinfection—defined as recurrent UTI caused by an infection that has been treated and subsequent repeat infection with the original bacteria or a second or new isolate [6]. Figure 14.3 illustrates an algorithm for management of recurrent UTIs [11].

Complications of UTIs include:

Urosepsis: Complicated and severe UTI occurring in the setting of a systemic inflammatory response syndrome (SIRS). It causes multiple organ dysfunction (acute respiratory distress syndrome, acute kidney injury (AKI), and disseminated intravascular coagulopathy (DIC)). In 20–30% of patients with sepsis, the urinary tract is the source; the estimated global mortality rate

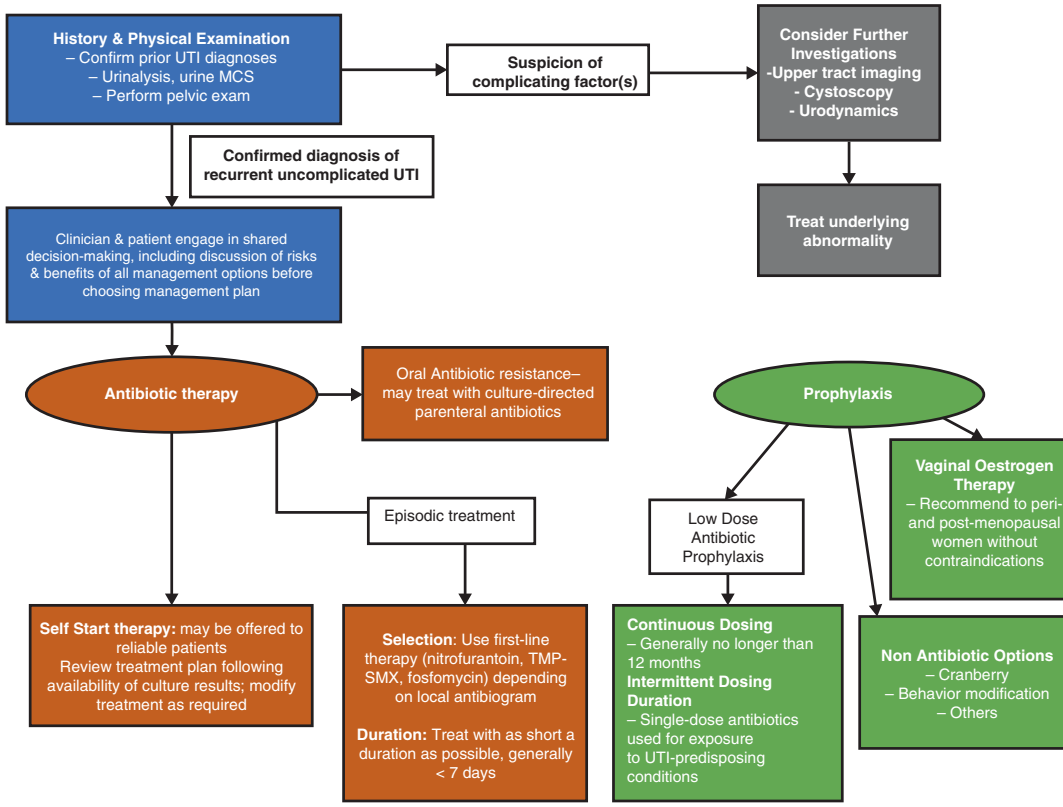

Fig. 14.3 Algorithm for management of recurrent uncomplicated urinary tract infections [11]. The target patient group is of otherwise healthy adult females with recurrent uncomplicated UTIs; Patients with complicating factors such as listed below are outside the scope of the pathway: (1) Anatomic or functional abnormality of the urinary tract, (2) Immunocompromised host, (3) Multi-drug resistant bacteria. *MCS* microscopy, culture & sensitivities, *TMP-SMX* trimethoprim-sulfamethoxazole, *UTI* urinary tract infection

for sepsis is about 30–40% [18]. The management of urosepsis is outlined in Table 14.2. Predisposing factors include urological anomalies, stones, urinary tract obstruction and, in male children, posterior urethral valves.

Other complications of UTI include kidney abscess, perinephric abscess, infected hydronephrosis/pyonephrosis, acute focal bacterial nephritis, emphysematous and xanthogranulomatous pyelonephritis, and malakoplakia.

Reflux Nephropathy

Reflux nephropathy has replaced the term 'Chronic pyelonephritis', a term that has become obsolete.

Aetiology

Reflux nephropathy is a result of an abnormality at the uretero-vesical junction. The musculature of the lowermost part of the normal ureter prevents reflux of urine from the bladder into the ureter. Failure at the vesico-ureteric junction means that urine passes up the ureter on bladder emptying, and in some patients there is free reflux, even when the bladder is not contracting. This is known as vesico-ureteric reflux (VUR).

Background

Until the 1970s, reflux nephropathy was known as 'chronic pyelonephritis', and was thought to be a chronic progressive condition. It was also thought that each urinary infection was capable of producing a scar, and furthermore that reflux

nephropathy caused hypertension. In the 1970s, Dr. Jean Smellie challenged the nephrological world to show that new scars could arise in adulthood: no such developing scars were found. It became clear that the scarring process took place mainly in the first 5 years of life, and that the change in kidney shape and the 'development of scars' during teenage years was simply the result of normal growth of the unaffected kidney tissue, thereby making the existing scarred elements more prominent.

Clinical Management

The abnormality is sometimes first detected *in utero,* when urine may be seen entering the foetal ureter during micturition. This will enable the neonatologist to take appropriate measures to prevent urinary infection in the neo-natal period.

A proportion of young children will present with a febrile illness that may not be recognised initially as a urinary tract infection. It is important to establish such a diagnosis, so that measures can be implemented to keep the urine sterile; this involves keeping the bladder empty. If a significant volume of urine refluxes up the ureter(s), there will inevitably be urine in the bladder after micturition (residual urine). One method in older children is to advise double micturition: the volume passed on the second occasion will give some idea of the scale of the reflux. If necessary, the bladder can be emptied again to be sure that the bladder is empty.

Investigations

VUR is diagnosed by the demonstration of backflow of urine into the upper renal tract(s). Historically, the diagnosis has been made by micturating cystourethrography, which provides good anatomical detail, but does require bladder catheterisation. For older children, indirect radionuclide cystography is preferable, as it does not require catheterisation.

Clinical Features in Adults

Typically in adults, the signs of reflux nephropathy will be found as an incidental finding on abdominal imaging: there will be one or more cortical scars overlying an anatomically distorted calyx, involving one kidney or both. In most cases the vesico-ureteric reflux will have remitted, and the urine will be sterile. In the absence of other factors (such as hypertension), the kidney function will remain relatively stable, and the number of adults requiring kidney replacement therapy (KRT) is small. Chronic kidney disease in this setting tends to progress when there is significant proteinuria (secondary FSGS), when hypertension is not well controlled, or when UTIs continue to recur.

Practice Point 1 Congenital Abnormalities of the Kidneys and Urinary Tract [CAKUT]

CAKUT encapsulates the various congenital urinary tract abnormalities that—although arising in childhood—sometimes present in adulthood, including vesicoureteric reflux. They include duplex pelvicalyceal systems, horseshoe kidney, pelvic kidney, mega-ureter, posterior urethral valves and a number of other uncommon disorders [19]

Mycobacterial Infections

Tuberculosis

Tuberculosis (TB) has a world-wide distribution, but is especially common in developing countries. The highest incidence rates are in sub-Saharan Africa and in the region stretching from the Indian subcontinent to South-East Asia and the Western Pacific (Fig. 14.4). In 2018, ten million people became ill with TB; 1.5 million of them died [21]. The emergence of multi-drug resistant TB as a co-infection with HIV/AIDs has made TB a major public health challenge. Extra-pulmonary TB (ETB) is estimated to occur in 10–34% of patients who do not have HIV, compared to about 50–70% in patients with HIV/AIDs [22].

Kidney involvement occurs as part of a disseminated infection, or as localized genitourinary disease. The disease causes extensive papillary necrosis and cavities, destroying the kidney parenchyma, and extending to the collecting sys-

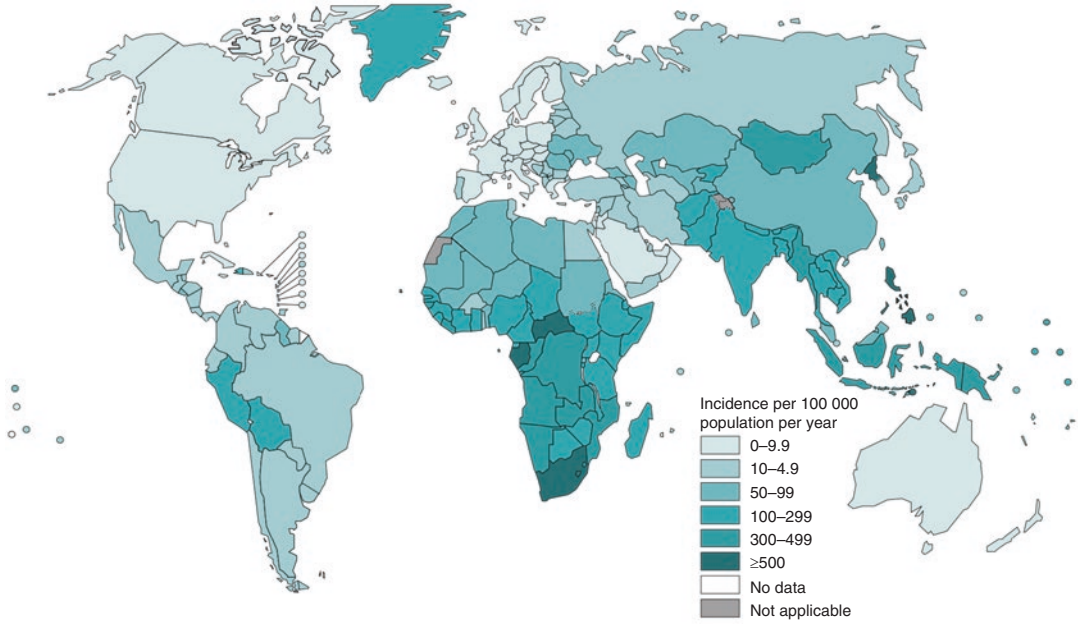

Fig. 14.4 Global Incidence of Tuberculosis in 2020; reproduced with permission from the World Health Organisation (WHO) [20]

tem, causing obstructive uropathy and kidney impairment. Management of genitourinary TB is outlined in Table 14.3. Glomerulopathy (like focal proliferative glomerulonephritis) and amyloidosis can occur from TB occurring in any part of the body [23]. Patients on KRT (haemodialysis, peritoneal dialysis and following kidney transplantation), and those on immunosuppressive therapy are particularly prone to TB infection.

Classical Uro-Genital Tuberculosis (UGTB)

Clinical Features

Uro-genital tuberculosis (UGTB), which is estimated to affect 6–8% of patients with TB, is easy to overlook. Systemic symptoms are uncommon. Often, lower urinary symptoms draw attention to the urinary tract, and typically there is pyuria, but no growth on culture using standard media—a so-called 'sterile' pyuria. Other reasons for the finding of a sterile pyuria are listed in Table 14.4.

The suspicion of TB may be aroused when the symptoms are not relieved by conventional antibiotics, however, there are sometimes suggestive symptoms - back, flank and suprapubic pain, macroscopic haematuria, frequency, and nocturia. Unlike newly-presenting TB, fever, weight loss and night sweats are unusual, and only a third of patients have an abnormal chest X-ray.

Table 14.4 Causes of a 'sterile' pyuria

• Tuberculosis of the uro-genital tract (UGTB)
• *Chlamydia trachomatis, Mycoplasma, Ureaplasma* infection
• Chemically-induced cystitis
• Kidney calculi, prostatitis
• Coliform [or other pathogen] UTI in the presence of antibiotic (inhibiting culture growth)
• Failure to realize that low numbers of organisms can indicate infection
• WBC from outside urinary tract, e.g. from foreskin or vulva
• Kidney parenchymal cause—e.g. acute TIN, glomerular disease

TIN tubulo-interstitial nephropathy, *UGTB* uro-genital tract tuberculosis, *UTI* urinary tract infection, *WBC* white blood cells

Investigations

Abdominal X-ray may show calcification, and urinary tract ultrasound is likely to show focal fibrosis and/or scarring—sometimes severe—as

well as calcification in kidneys and bladder (thimble bladder).

Treatment

For newly presenting TB, the World Health Organisation (WHO) recommends oral treatment for 6 months, commencing with 4 drugs, that should include rifampicin and isoniazid (Table 14.3). In patients with kidney dysfunction, careful attention needs to be taken regarding the dosing of the drugs prescribed.

Tuberculous Interstitial Nephritis

There have been a number of reports of interstitial nephritis with granuloma formation, and there has been a suspicion that TB has been responsible. Some patients have had TB elsewhere and hypersensitivity to tuberculin. An early report described three such patients [24]. More recently, it has become clear that such patients cannot reliably be distinguished from sarcoidosis, and it has been suggested that a trial of anti-tuberculous drugs can be justified [25].

End-Stage Kidney Disease

Once TB is recognized and treated, it is likely that kidney replacement therapy (KRT) can be avoided. There are very few data on the frequency of TB as a cause of end-stage kidney disease (ESKD), but there is one report using data from the European Dialysis and Transplant Registry. Analysis of data from 5 years between 1984 and 1991 showed that the primary kidney diagnosis was classified as kidney TB [code 91] in 0.5–1.0% of patients starting KRT [26].

Leprosy

The incidence and prevalence of leprosy has been falling slowly over recent years but there has been little change in the global extent of the disease. It remains more or less confined to middle- and low-income countries, especially Brazil and the countries of the Indian sub-continent (Fig. 14.5).

Clinical Features

Kidney involvement is common in leprosy, and it is now clear that it is the multi-bacillary (lepromatous) form that is most closely associated with kidney disease. A study of 199 autopsies from Brazil showed that 144 [72%] had kidney lesions. Sixty-one of the 144 (42.4%) showed amyloidosis [28]. This included 36% of the lepromatous group but only 5% of the tuberculoid and

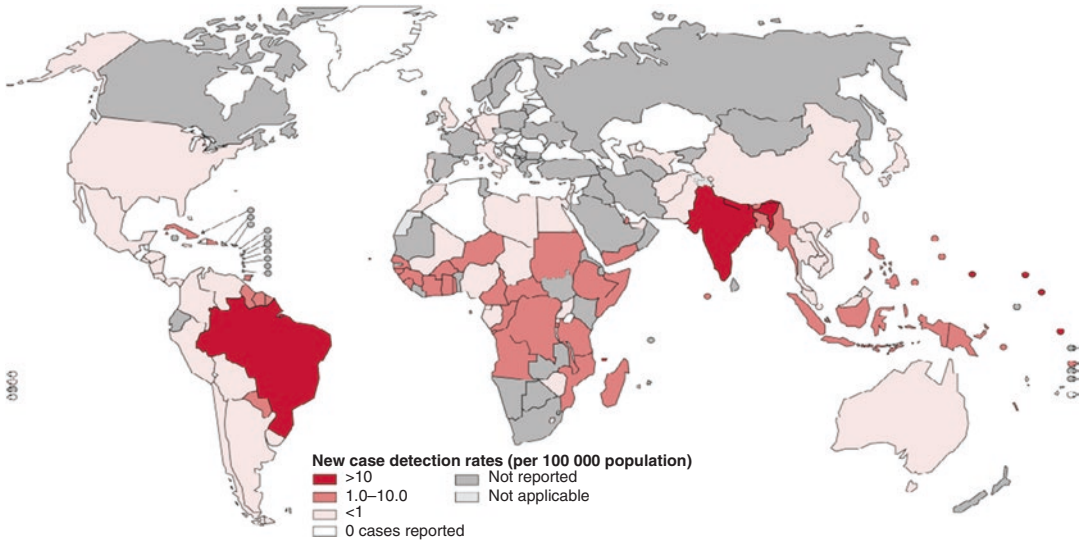

Fig. 14.5 Leprosy new case detection rates 2016 reproduced with permission from the World Health Organisation (WHO) [27]

borderline cases. It was noted that during flare-ups of erythema nodosa leprosum, the serum creatinine would tend to rise.

Silva et al. reported on 16 studies of kidney disease in patients with leprosy [29]. Excluding 10 studies where there was either no biopsy or fewer than five patients, there were 354 biopsies in 6 studies. All six mentioned amyloidosis as the prominent diagnosis; many of the patients described had proteinuria.

There are a few reports of glomerulonephritis among patients with leprosy but there is no consistent pattern, and such associations are as yet unproven.

Treatment

The WHO recommends a 3-drug regimen for multi-bacillary [lepromatous] leprosy - rifampicin, clofazamine and dapsone. The recommendation for pauci-bacillary leprosy [tuberculoid] is a 2-drug regimen - rifampicin and dapsone. Rifampicin and dapsone do not require dose reduction in patients with reduced GFR; for Clofazimine, the UK British National Formulary (BNF) states "Use with caution".

Leptospirosis

Leptospirosis is a zoonotic disease, which is re-emerging as an infectious disease of global public health importance. It affects approximately 1.03 million people annually and it is projected to rise further as extreme climatic conditions and global warming increase [30].

Leptospirosis Kidney Disease: Acute leptospirosis causes multiple organ dysfunction including AKI. A long-term follow-up study of leptospirosis AKI patients in Sri Lanka found that 9% of them developed an early stage of CKD [31], indicating that leptospirosis AKI can result in CKD/ESKD.

Asymptomatic carriers harbor the Leptospira spirochaete in the kidney where they colonize the proximal tubule resulting in chronic tubulointerstitial nephritis and fibrosis causing insidious progression to CKD. It is thus suggested that asymptomatic exposure to leptospira infection carries the risk for CKD. Histologic findings in leptospirosis kidney disease are tubulointerstitial nephritis, interstitial fibrosis, and tubular atrophy. Proximal tubule dysfunction and hypokalaemia are seen also in adult male patients with leptospirosis. These bear a characteristic similarity to findings in CKD of unknown aetiology (CKDu), a form of CKD that clusters amongst farmers who work in hot dry climates. Table 14.3 outlines the diagnosis and management of leptospirosis.

Practice Point 2 Leptospirosis Kidney Disease and CKDu Overlap

Leptospirosis kidney disease and CKDu tend to affect similar populations in similar geographical regions. The similarity of their kidney pathologies has put leptospirosis as a priority candidate for some patients with CKDu. It is postulated that secondary injury from heat stress and dehydration worsens the kidney injury. Thus, leptospira infection causes primary kidney disease or acts as a CKD susceptibility factor.

Indirect or Immune-Mediated Damage to the Kidney

Indirect bacteria-related damage to the kidney occurs as inflammation of the glomerulus due to immune complex deposition. Infection related GN (IRGN) was previously known as postinfectious GN (PIGN); the prototype, poststreptococcal GN (PSGN) commonly occurs in children. PIGNs are mainly caused by streptococcal infections (28–47%), while staphylococcal and gram-negative infections account for 12–24% and 22%, respectively [32]. Other infections, such as bacterial endocarditis and shunt infections can also cause a PIGN.

Bacterial Infection-Related Glomerulonephritis (B-IRGN)

B-IRGN is described as kidney dysfunction from glomerular inflammation, with evidence of ongoing bacterial infection, unlike PSGN which occurs weeks after the infection. The incidence of IRGN, though decreasing, constitutes about 5% of all glomerular diseases [33]. It occurs more frequently in developing countries. It is commoner in adults, with much higher rates in the elderly and patients with diabetes. Other risk factors include malignancy, malnutrition, chronic infections (HIV and TB), and prosthetic heart valves. IRGN can result from infections occurring in any part of the body (skin, upper and lower respiratory tract, heart, urinary tract, bone). Many bacterial species can be involved, but staphylococcal species are more common in adults and the elderly.

The most common presentation is an acute nephritic syndrome, with or without impaired kidney function. B- IRGN has poorer prognosis than PSGN, and also has a poorer prognosis in adults than in children [32, 33]. Early detection and treatment of infections can prevent kidney involvement (Table 14.5).

Post-streptococcal GN (PSGN)

PSGN is diagnosed in a patient with antecedent streptococcal infection who presents with acute GN; for streptococcal sore-throat, the nephritis follows 7–15 days afterwards, while for skin infections 4–6 weeks after (see Clinical Scenario 2). PSGN is an immune-mediated GN triggered by immune-complex deposits in the subendothelium and mesangium comprising of bacterial antigens (glyceraldehyde-3-phosphate dehydrogenase and streptococcal pyrogenic exotoxin B).

The most common clinical manifestation is acute nephritic syndrome which lasts <2 weeks. Other less common manifestations are asymptomatic proteinuria, nephrotic syndrome or rapidly progressive GN. The prognosis in children is excellent, but in the elderly, there is an associated mortality of up to 20% [32]. The long-term prognosis is worse in patients who have persistent proteinuria >6 months. Clinical Scenario 2 illustrates a typical presentation of severe PSGN, in a patient in Nigeria, although many patients are seen with a less severe presentation. The management of PSGN is outlined in Table 14.5.

Kidney Injury as Part of Ongoing Sepsis

One of the commonest ways by which bacterial infections cause kidney dysfunction is through AKI, which occurs as part of multi-organ dysfunction following sepsis from any focus. About 20% of very ill patients have irreversible kidney injury from acute cortical necrosis and many more (40%) progress to CKD following incomplete recovery [34]. Often, these patients have pre-existing mild-moderate CKD from diverse causes. AKI incidence increases according to severity of sepsis, from 4.2% in mild sepsis to 22.7% in severe sepsis and rising to 52.8% in septic shock [35]. Table 14.3 outlines the management of sepsis/urosepsis.

Nephrotoxic Damage from Medications, Used in Patients with Infection

Drugs commonly cause kidney damage and drug-induced nephrotoxicity (DIN) occurs in 14%–26% and 16% of AKI in adult and paediatric populations respectively [36]. It is commoner in older patients, who are more likely to have diabetes and cardiovascular disease and are consequently exposed to several medications and diagnostic procedures that can harm the kidney. Antibiotics and other medications like non-steroidal anti-inflammatory drugs (NSAIDs) useful in treatment of bacterial infections are known to be nephrotoxic. Table 14.6 shows the common mechanisms leading to drug-induced nephropathy and some implicated medications.

Factors that increase the risk of nephrotoxicity include intravascular volume contraction, age > 60 years, diabetes, use of multiple nephrotoxins, heart failure, sepsis, underlying kidney impairment.

Prevention, vigilance, recognition and early intervention are key to successful outcome [37].

Table 14.5 Investigations and management of other bacterial infection-related kidney diseases: bacterial infection-related glomerulonephritis (B-IRGN), post-streptococcal glomerulonephritis (PSGN) and nephrotoxic damage

Category	Bacterial infection-related GN	Post-streptococcal GN	Nephrotoxic damage
Investigations	Histological findings: membranoproliferative GN, diffuse proliferative GN, or mesangioprolifertive GN with or without crescents	Urinalysis ASO titre Kidney function tests—creatinine, urea/blood urea nitrogen (BUN) C3 complement Kidney biopsy is not indicated except when diagnosis is in doubt. Histology demonstrates acute endocapillary GN with mesangial and capillary granular immune deposition	Urinalysis Complete blood count Kidney function tests Liver function tests
Treatment and Follow-up	Identify and eradicate the infection using appropriate antibiotics Manage complications Immunosuppression is not recommended	Early antibiotic therapy (penicillin, or erythromycin) to help resolve infection Hypertension and oedema respond to diuresis. Admit patients who have severe hypertension or congestive heart failure Serum C3 should normalize in 8–10 weeks; if hypocomplementaemia persists beyond 3 months, perform kidney biopsy Proteinuria persisting beyond 6 months, use ACE-I or ARBs Patients who have extensive glomerular crescents/RPGN should receive pulses of intravenous methylprednisolone Note: antibiotics do not reverse GN	Prevention is crucial: Institute measures to prevent nephrotoxicity: Estimate patient's baseline renal function before prescribing medications (where appropriate monitor blood levels). Avoid combining nephrotoxic agents Check and correct risk factors for nephrotoxicity before initiating therapy Ensure adequate hydration before and during therapy or diagnostic procedures Vigilance, recognition and early intervention are key to successful outcome At first sign of nephrotoxicity, withdraw offending medication Support blood pressure and maintain adequate hydration

Table 14.6 Mechanisms of drug-induced nephropathy

Mechanism of kidney damage	Medications
Disruption of intra-glomerular haemodynamics	ACEIs; ARBs; Cyclosporine
Hypersensitivity	Beta-lactams; Quinolones; Rifampicin; Sulfonamides; Vancomycin
Inflammation	NSAIDs
Tubular cell toxicity	Aminoglycosides; Amphotericin B; Tenofovir
Crystal nephropathy	Ampicillin; Ciprofloxacin; Sulfonamides
Rhabdomyolysis/Haemolysis	Triamterene
Thrombotic microangiopathy	Benzodiazepines; Statins; Clopidogrel; Cyclosporine

ACEIs Angiotensin converting enzyme inhibitors, *ARBs* Angiotensin receptor blockers, *NSAIDs* non-steroidal anti-inflammatory drugs

Awdishu and Mehta proposed the 6R approach (Risk assessment, early Recognition, targeted Response, timely Renal support and Rehabilitation coupled with Research) for management of DIN [38]. Table 14.5 outlines the investigations and management of infection-related kidney damage due to nephrotoxic damage.

Viral Infections and the Kidney

Viral infections can cause kidney damage through direct viral invation, immune mediated damage, haemodynamic instability, haemolysis, rhabdomyolysis, and cytokine storm, amongst other mechanisms. Table 14.7 summarises the viruses associated with kidney damage, the mechanism of injury, typical kidney involvement and management of the condition.

Dengue Virus

Dengue virus (DV) infection causes widespread capillary leakage, dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) resulting in ischaemic acute tubular necrosis. Direct viral cytopathic effects, and immune complex injury, haemolysis and rhabdomyolysis are other mechanisms of kidney disease [39]. Clinical manifestations vary from asymptomatic urinary abnormalities to severe acute kidney injury(AKI) in native and allograft kidneys [40]. Proteinuria occurs in over 70%, whereas haematuria is less frequent in DHF. Kidney involvement occurs during acute infection, with detectable anti-DV antibodies and viral nucleic acid in plasma. AKI is more frequent in DHF and DSS and is associated high mortality. Kidney biopsy may reveal acute tubular necrosis, interstitial nephritis and various immune complex GN, as shown in Table 14.7. DV antigen may be detected in tubular epithelial cells [41]. Management is supportive with fluid resuscitation, control of metabolic derangements and management of coagulopathies. Kidney outcomes are good; however, proteinuria and haematuria may persist after recovery of AKI [42].

Hantavirus

Hantavirus(HV) infection is associated with increased vascular permeability and haemorrhage leading to organ dysfunction, with kidney involvement reported in 30–60% of cases, especially in hantavirus haemorrhagic fever with renal syndrome(HFRS) [43]. Kidney disease occurs in the course of active infection from direct viral invasion of tubular epithelial cells, glomerular endothelial cells and podocytes [44]. Systemic inflammatory and immune complex deposition may also contribute to kidney disease. Oliguric AKI with haematuria and sub-nephrotic proteinuria, followed by polyuria is the usual clinical presentation in HFRS. Milder forms of kidney dysfunction may be seen in the other Hanta virus syndromes. Kidney histopathology shows acute haemorrhagic interstitial nephritis with mononuclear cell infiltrates (CD8+ T-lymphocytes and macrophages), tubular necrosis and congestion of peritubular capillaries, especially in the outer medulla [45]. Glomerular lesions have also occasionally been reported; (see Table 14.7). Management is mainly supportive with antipyretics, fluid resuscitation, control of electrolyte disorders, vasopressors and KRT when indicated. Kidney recovery is usual; however, hypertension, cardiovascular disease, hypopituitarism and chronic kidney disease of unknown aetiology have been reported in those who recover [46, 47].

Ebola Virus

Ebola infection is marked by uncontrolled viral replication, which results in excessive proinflammatory responses, endothelial dysfunction, and dysregulation of the coagulation cascade, haemorrhage and subsequently severe organ dysfunction. Viral invasion of tubular and endothelial cells, systemic complications of the infection, and bacterial and malarial super infection result in kidney involvement [48]. Acute kidney injury is the main manifestation in 20–50% of cases. AKI is multifactorial, as outlined in Table 14.7. Kidney biopsy is not

Table 14.7 Kidney involvement in viral infections

Virus	Mechanism of kidney injury	Kidney involvement	Management
Acute			
Dengue	Direct viral invasion Immune-mediated, haemodynamic instability, haemolysis, rhabdomyolysis	ATN, ICGN, MesPGN TMA, AIN, IgA, pre-renal azotaemia	Supportive care, fluid resuscitation
Hantavirus HFRS	Direct viral invasion Immune-mediated haemolysis, rhabdomyolysis, volume depletion	ATN, MesPGN, AIN, pre-renal azotaemia	Supportive treatment, fluid resuscitation, dialysis without heparin
Ebola	Direct viral invasion, haemodynamic instability, Cytokine storm, coinfection with malaria, gram negative septicaemia	ATN, DIC, pre-renal azotaemia	Supportive treatment, fluid resuscitation, dialysis without heparin
Varicella-zoster	Immune-mediated Direct invasion	DPGN, TMA, HSP, MPGN, microscopic polyangiitis, AIN ATN, RPGN	IV Acyclovir 10 mg–20 mg/kg bodyweight for 2 weeks, then orally for 3 months in renal allograft recipients Supportive care
Parvovirus	Direct viral invasion Immune-mediated	ICGN, PAN, TMA, HSP, microscopic polyangiitis, TIN acute renal allograft rejection	Supportive care
Hepatitis A	Immune-mediated	ICGN, mesPGN, ATN, Pre-renal azotaemia	Supportive care, fluid resuscitation,
Hepatitis E	Direct viral invasion	ATN, Pre-renal azotaemia	Supportive care, fluid resuscitation.
Hepatitis B	Immune-mediated Systemic effects of infection	MN, MPGN, IgA, ATN, DPGN, RPGN	NAs, pegylated interferon, supportive care **RPGN**: NA + corticosteroids + cyclophospamide/ rituximab
Cytomegalovirus	Direct viral invasion Immune complex	cFSGS, MN, IgA, HSP, ICGN, MPGN, TMA, RPGN	Valganciclovir 900 mg/12 hourly per os; IV Ganciclovir 5 mg/kg/12 hourly for 14–28 days or for refractory disease; forscanet 90 mg/kg/12 h; IV immunoglobulins; or cidofovir. Prophylactic valganciclovir 900 mg/daily for a further 30 days

ATN acute tubular necrosis, *ICGN* immune complex glomerulonephritis, *MesPGN* mesangial proliferative glomerulonephritis, *DPGN* diffuse proliferative glomerulonephritis, *cFSGS* collapsing focal glomeruloscleroses, *ncFSGS* non-collapsing focal segmental glomeruloscleroses, *MN* membranous nephropathy, *IgA* Immunoglobulin A, *HSP* Henoch Schoenlein purpura, *HFRS* hemorrhagic fever and renal syndrome, *MPGN* membranoproliferative glomerulonephritis, *MC* mixed cryoglobulinemia, *TMA* thrombotic microangiopathy, *DIC* disseminated intravascular coagulopathy, *HIVAN* HIV-associated nephropathy, *HIVICK* HIV immune complex disease of the kidney, *PAN* polyarteritis nodosa, *RPGN* rapidly progressive glomerulonephritis, *UTI* urinary tract infection, *DAAs* direct acting antivirals, *IS* immunosuppressive agents, *IV Ig* intravenous immunoglobulins, *cART* combined antiretroviral therapy, *RAAS* renin angiotensin aldosterone system, *SARS-CoV-2* severe acute respiratory syndrome-coronavirus-2, *MGRS* monoclonal gammopathy of renal significance, *TIN* tubulo-interstitial nephritis, *AIN* acute interstitial nephritis, *DILS* diffuse infiltrative lymphocytic syndrome, *IRIS* immune reconstitution syndrome, *NA* nucleos(t)ide analogs (Lamivudine, telbivudine, tenofovir, adefovir)

routine for diagnosis; however, acute tubular necrosis and degeneration with interstitial oedema and mild cellular infiltrates have been reported on kidney histology [49]. Aggressive fluid resuscitation and usual care for AKI, including KRT is the mainstay of management, with particular consideration of staff safety [50].

Parvovirus

Symptomatic parvovirus B(PVB) infection occurs in 2–12% of patients in the first year of kidney transplantation, with 10% of these developing allograft dysfunction [51]. PVB kidney disease may also occur in native kidneys of immunocompetent individuals. Direct invasion of kidney tissue and immune-mediated kidney injury are the main disease mechanisms [52]. Acute nephritic syndrome with hypocomplementaemia, following a prodrome of rash, fever, and arthritis is frequent. Nephrotic syndrome or chronic kidney disease is seen in sub-acute infection; and aplastic crisis may follow the nephrotic syndrome in patients with sickle cell disease [53]. Endocapillary and mesangial proliferation with subendothelial deposits of C3 and IgG, suggestive of acute post-infectious glomerulonephritis is frequent on kidney histopathology [54]. Other histological lesions seen on kidney biopsy are shown in Table 14.7. Viral antigens are often present in blood and may be detectable in kidney tissue. Management is supportive; and is often combined with reduction of immunosuppression and administration of intravenous immunoglobulins in transplant recipients with persistent infection [55].

Polyoma Virus

Polyoma virus nephropathy (PVN), caused mainly by the BK virus, occurs in 1–10% of kidney transplants, causing graft loss in about 50% of these cases [56]. PVN is rare in native kidneys of non-kidney organ recipients. Viral replication in the kidney epithelium causes a tubulointerstitial nephritis [57]. The major risk factor for PVN is intense immunosuppression; however, patient, organ, viral and other immunity-related risk factors may play a role. Nephropathy follows viraemia, resulting from latent viruria [58]. PVN often presents as asymptomatic worsening of kidney function, and/or chronic graft dysfunction in the first year of transplantation. The diagnosis of PVN requires urine cytology, urine and plasma BK viral load and kidney biopsy. Viral inclusion bearing epithelial cells called 'decoy cells' may be present on urine cytology. Decoy cells $\geq$10/cytospin [59], a urine BK viral load $>10^7$ copies/mL and a plasma BK viral load $>10^4$ copies/mL [60, 61] are indicative of a presumptive diagnosis of PVN. Kidney biopsy remains the diagnostic gold standard. Three histological patterns of patchy tubulo-interstitial nephritis with varying degrees of viral cytopathic changes, interstitial inflammation, and in late stages, tubular atrophy and interstitial fibrosis are observed [62]. Three classes of PVN based on tissue replication load, and interstitial fibrosis(ci) score have been described [63]. Reduction of immunosuppression (IS) is the mainstay of management, with addition of antiviral agents in refractory cases. Various algorithms of stepwise and careful reduction of antimetabolites and calcineurin inhibitors are in use. Some antiviral agents, and fluoroquinolones and intravenous immunoglobulins may be useful in refractory PVN. Re-transplantation is possible after graft loss when the viral load becomes undetectable [64, 65].

Cytomegalovirus

Cytomegalovirus (CMV) nephropathy occurs in both immunocompetent and immunocompromised individuals, and results from viral replication in kidney cells and immune complex mediated injury [66]. CMV infection is common after kidney transplantation, where it adversely affects graft and patient survival [67]; however, CMV nephropathy is rare, occurring in <1% of transplanted patients [68]. Kidney disease often occurs during acute systemic CMV illness, following reactivation of latent infection in the

setting of intense immunosuppression, or less often during primary infection. The usual clinical manifestation is acute kidney injury with or without haematuria, and varying degrees of proteinuria. Nephrotic syndrome is infrequent. Diagnosis is based on the presence of viral cytopathic changes in kidney tissue, usually in the presence of CMV viraemia. A high viral load of >10,000 copies/mL seems to correlate with CMV nephropathy [69]. Kidney histopathology shows patchy acute or chronic peritubular pleomorphic mononuclear interstitial infiltrates with tubulitis; tubular epithelial cells are markedly enlarged with characteristic intranuclear eosinophilic inclusions ('owl eye' type inclusions). Viral particles may be seen in both the nuclei and cytoplasm of infected cells, and CMV is present on immunostaining [70]. Glomerular and vascular lesions may occur either in coexistence with tubulo-interstitial disease or in isolation (Table 14.7). Management of CMV nephritis in kidney allografts involves the use of antiviral agents, reduction of immunosuppression and use of immunomodulators [71] (Table 14.7). CMV nephritis is usually mild and self-limiting in immunocompetent patients.

Varicella Infections

Kidney involvement in varicella zoster virus (VZV) infection is rare and occurs essentially during primary infection in both native and allograft kidneys [72, 73]. Kidney disease is mediated through viral immune complex injury and dysregulation of complement activity [74, 75]. Clinical manifestations include acute glomerulonephritis syndromes, nephrotic syndrome, atypical haemolytic uraemic syndrome, vasculitis and acute kidney injury. Kidney biopsy findings are shown in Table 14.7. Acyclovir, together with supportive care for kidney syndromes is usual care.

Hepatitis E Virus

Kidney disease, essentially glomerulonephritis (GN) is association with acute and chronic hepatitis E virus (HEV) infection in both immunocompetent and immunocompromised individuals [76]. Immune- mediated mechanisms and direct viral cytopathic effects may contribute to kidney damage [77]. A monoclonal gammopathy of renal significance presenting as light chain cast nephropathy was recently reported [78]. Acute kidney failure and the nephrotic syndrome are the usual clinical presentation. In kidney allograft recipients, HEV is associated with proteinuria and a decline in glomerular filtration rate [79]. The spectrum of lesions reported on kidney biopsy are shown in Table 14.7. Treatment is supportive, however in kidney allograft recipients, reduction in immunosuppression and use of ribavirin for 3–6 months are the mainstay of treatment.

Hepatitis A

Hepatitis A virus (HAV)-associated kidney disease occurs in both non-fulminant and fulminant disease, manifesting essentially as AKI with acute tubular necrosis as the main mechanism [80]. Immune-complex-mediated injury, and direct viral cytopathic effects are other suggested mechanisms of kidney pathology [81]. The diagnosis is based on laboratory evidence of infection, in the presence of clinical features consistent with any of the kidney syndromes. Kidney biopsy is rarely required for diagnosis, except with an atypical presentation**.** Oher mechanisms of AKI and histopathological findings are shown in Table 14.7. Management is supportive and aimed at improving kidney perfusion, and treating complications of kidney syndromes. Kidney recovery is frequent, even in dialysis-requiring AKI.

Hepatitis B Virus

Hepatitis B virus (HBV)-associated nephropathy remains frequent in HBV endemic zones, and occurs mainly with chronic HBV infection. Glomerulonephritis (GN) and polyarteritis nodosa (PAN) from immune-mediated and possible direct viral effects are the main presentations [82]. Consequences of severe liver disease may cause AKI [83]. GN may present

with proteinuria, nephrotic syndrome, microscopic haematuria, hypertension or kidney impairment, with the latter unusual in children. HBV DNA, and serological markers of HBV infections are often present in serum, however HBV GN has been reported in HBsAg seronegative patients [84]. Hypocomplementaemia may exist with MPGN and PAN, whereas mixed cryoglobulinaemia is rare. MN, MPGN and MesPGN are the main histological patterns. MN is common in children whereas MesPGN is common in adults and may coexist with MN. Sub-epithelial, sub-endothelial and mesangial deposits of IgG with C3, IgA, IgM and C1q are frequent and immune complexes may contain HBsAg and HBeAg and HBcAg. Other forms of GNs have been reported in adults [85] (Table 14.7). Treatment is with antiviral nucleos(t)tide analogs(NAs). Immunosuppressive agents, pegylated interferon and plasma exchange maybe added to NAs in PAN and rapidly progressive GN [86], as shown in Fig. 14.6. Spontaneous remission is frequent in children with clearance of HBeAg whereas about a third of adults with HBV GN eventually develop chronic kidney failure [85].

Hepatitis C Virus

Hepatitis C virus (HCV) nephropathy is essentially immune complex mediated GN and vasculitis [87]. The pathological hallmark of HCV-GN is type I MGPN with or without type 2 mixed cryoglobuinaemia [33]. HCV GN presents as an acute nephritic syndrome, varying degrees of albuminuria or rapidly progressive GN, with presence of viral RNA and anti-HCV antibodies in serum. Cryoglobulinaemia occurs in 50–70% and it is associated will low early complement components (C4, C1q, CH50). Kidney histology typically shows MPGN with mononuclear, polymorphonuclear leucocyte infiltrates, and subendothelial deposits of IgG, IgM and C3 [88]. Other glomerular lesions and vascular lesions have

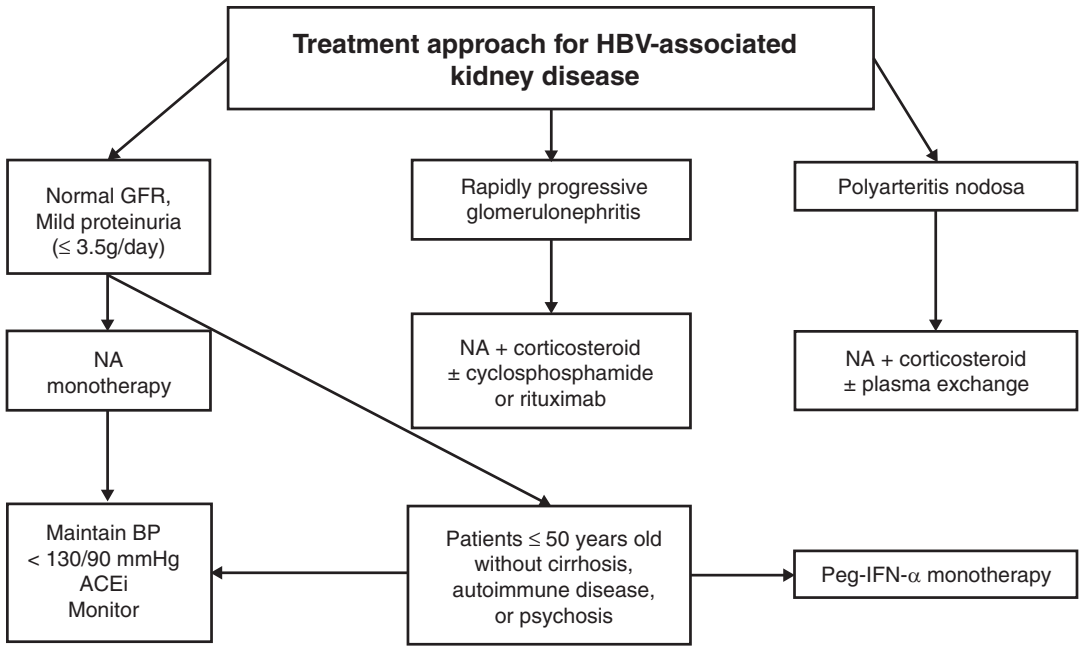

Fig. 14.6 Algorithm showing treatment approach to Hepatitis B-associated kidney disease. [*BP* blood pressure, *GFR* glomerular filtration rate, *HBV* Hepatitis B virus, *NA* Nucleotide/Nucleoside antagonist, *ACEi* angiotensin converting enzyme inhibitor, *Peg-IFN-α* pegylated interferon-alfa]

been reported (Table 14.7). KDIGO has recommended the use of direct acting antivirals (DAAs) for HCV kidney disease, with the choice, dosage and duration of DAAs therapy based on HCV genotype, glomerular filtration rate, virologic response and possible drug interactions, as shown in Fig. 14.7 [89]. In addition to DAAs, it recommends the use of immunosuppressive agents (IS) with or without plasma exchange in case of a cryoglobulinaemic flare or nephrotic syndrome, with rituximab as first line IS for cryoglobulinaemic kidney disease.

Kidney function	HCV genotype	Recommended regimen(s)	strength of evidence	Alternate regimen(s)	Strength of evidence
CKD G4–G5 (GFR < 30 ml/min per 1.73 m^2) including HD, KTR[b]	1a	Grazoprevir/elbasvir	1B	Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir (also known as PrOD or 3D regmien) with ribavirin	2D
		Glecaprevir/pibrentasvir	1B	Dactatasvir/asunaprevir	2C
	1b	Grazoprevir/elbasvir	1B	Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir (also known as ProD or 3D regimen)	2D
		Glecaprevir/pibrentasvir	1B	Daclatasvir/asunaprevir	2C
	2,3	Glecaprevir/pibrentasvir	1B		
	4	Grazoprevir/elbasvir	2D		
		Glecaprevir/pibrentasvir	1B		
	5,6	Glecaprevir/pibrentasvlr	2D		
CKD G5 PD	n/a (reasonable to follow proposed regimens for HD)				
KTR (GFR ≥ 30 ml/min per 1.73 m^2)	1a	Sofosbuvir with ledipasvir, daclatasvir or simeprevir	1B	Sofosbuvir/ribavirin	2D
		Glecaprevir/pibrentasvir[c]	1C		
	1b	Solosbuvir with ledipasvir, daclatasvir or simeprevir	1B		
		Glecaprevir/pibrentasvir[c]	1C		
	2,3,5, 6	Glecaprevir/pibrentasvir[c]	1D	Sofosbuvir/daclatasvir/ribavirin[d]	2D
	4	Sofosbuvir with ledipasvir, daclatasvir or simeprevir	1D		
		Glecaprevir/pibrentasvir[c]	1D		

Fig. 14.7 Recommendation grades (1–2) and strength of evidence (**a**–**d**) are listed for each recommended treatment regimen and HCV genotype. (**a**) Recommended Hepatitis C virus (HCV) direct-acting antiviral (DAA) treatment regimens for patients with CKD G1-G5D and kidney transplant recipients (KTRs), by hepatitis C virus (HCV) genotype. (**b**) Treatment scheme for CKD stages G1-G5D patients with confirmed Hepatitis C infection. (**c**) Treatment algorithm for Kidney Transplant Recipients with confirmed Hepatitis C infection, by GFR and HCV genotype. *CKD* chronic kidney disease, *DAA* direct-acting antiviral, *GFR* glomerular filtration rate, *HCV* Hepatitis C virus, *NAT* nucleic acid testing

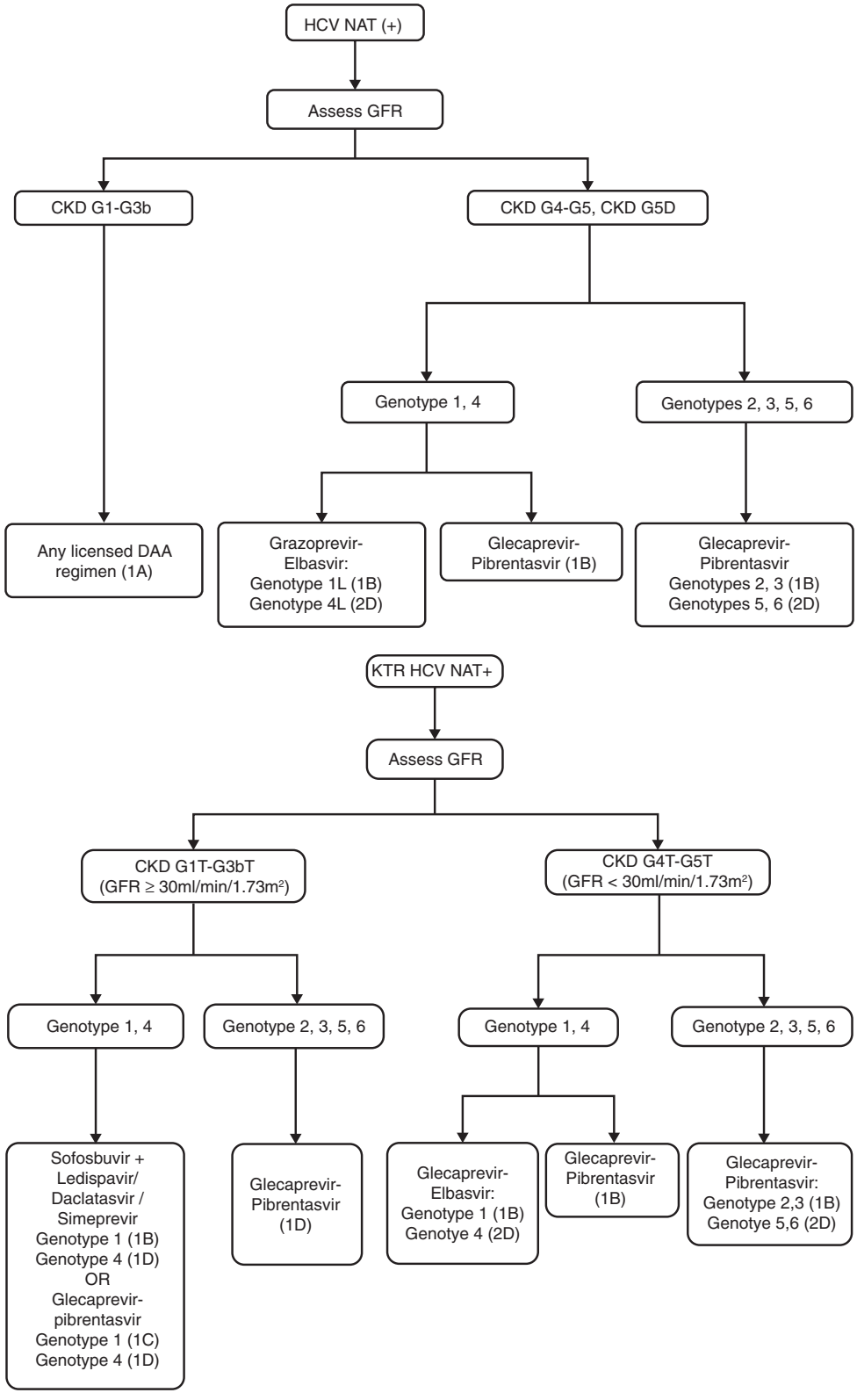

Fig. 14.7 (continued)

HIV

Both acute and chronic kidney disease are common in the course of HIV infection. Mechanisms of kidney injury in the course of HIV infection vary from direct viral cytopathic effects, immune complex disease, and systemic complications of immunodepression and infection or their therapies [90, 91]. The diagnosis of kidney disease in an HIV-positive patient must therefore consider whether patient is combination anti-retroviral therapy (cART)-naïve or not, and whether there is an ongoing co-infection. HIV-associated nephropathy (HIVAN), focal segmental glomerulosclerosis (FSGS) and HIV immune complex disease (HIVICK) are the main kidney manifestations of HIV infection. HIVAN, the most frequent cause of kidney disease in HIV-positive individuals of African descent, results from the cytopathic effects of the virus on visceral and parietal epithelial cells [92]. cART-naïve African blacks with apolipoprotein-1 (APOL-1) G1/G2 variants are especially at risk [93, 94]. The lifetime risk of developing HIVAN in an untreated HIV-positive black patient is 2–10%, but the risk rises to 50% if the patient is homozygous for APOL-I variants [95]. HIVAN typically presents with varying degrees of proteinuria or the nephrotic syndrome with progressive kidney failure. Histologically, classic HIVAN is characterized by collapsing glomerulopathy and attendant tubulointerstitial disease including tubular microcyst formation, interstitial inflammation and tubular injury [91]. HIVICK represents a heterogenous group of proliferative immune-complex mediated GN occurring in a patient with active HIV infection without other possible aetiologies. HIVICK usually manifests as a nephritic or nephrotic-nephritic syndrome in the absence of coinfections such as HBV or HCV. Various proliferative GNs are seen on kidney histology in HIVICK with a post-infectious GN histological pattern observed in about 50% of cases [96]. Other podocytopathies, tubulointerstitial and vascular diseases have been reported in the setting of HIV infection, as shown in Table 14.7. Management involves viral suppression with cART, and measures to slow progression of chronic kidney disease. Recommendations on the screening, management and monitoring of kidney disease in HIV-positive individuals were published recently [91].

Severe Acute Respiratory Syndrome Coronavirus-2 [SARS-CoV-2]

The global pandemic of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has affected millions of people around the world, and kidney disease is increasingly recognized as one of its serious complications. A study of 710 hospitalized patients in Wuhan, China with COVID-19 showed that 44% had proteinuria and haematuria, and 26.7% had haematuria on admission. The prevalence of elevated serum creatinine and blood urea nitrogen was 15.5% and 14.1%, respectively. AKI occurred in 5.1% and was associated with a four-fold increase in mortality [97]. A systematic review reported the incidence of AKI to be 8.9% in 6945 COVID-19 patients [98]. There was a higher risk of mortality (RR 3.08–4.19) in severe AKI (AKI Stage 3, or requiring KRT) was reported in a meta-analysis [99]. The proposed mechanisms of kidney injury are diverse, and include direct viral infection, effects on the renin-angiotensin-aldosterone system, haemodynamic instability, coagulopathy and cytokine storm [100]. Histology of native and allograft kidney biopsies in 17 patients in New York, 15 of whom presented with AKI, and 9 with nephrotic range proteinuria, showed that 5/14 native kidneys had collapsing glomerulonephritis (cGN); 2 with membranous GN; one each with minimal change disease, lupus nephritis with crescents, anti-GBM nephritis; and 4 with acute tubular injury (Table 14.7). The 3 allograft biopsies showed

acute T-cell mediated rejection, cortical infarction and acute tubular injury. Three patients with cGN (labelled as "COVAN") and one with minimal change disease were shown to have *APOL1* high-risk genotype [101]. In a study of 114 chronic haemodialysis patients from New York, intensive care unit (ICU) admission was required in 13.2% and 16.7% required mechanical ventilation with an overall mortality of 28%; of 86.7% of those requiring ICU, nearly 100% required mechanical ventilation [102].

Kidney transplant recipients appear to be at increased risk of severe COVID-19 disease and mortality rate of 28% was reported in one centre [103]. Treatment is supportive with supplemental oxygen, anticoagulation and dexamethasone for those requiring oxygen, with various agents under clinical trial (including remisidivir, tocilizumab). The vaccines against SARS Cov-2 have reduced the infection rates, severe infection, hospitalization and mortality. Randomised controlled trials to date have shown benefits of dexamethasone, tocilizumab, neutralizing antibodies, and remdesivir.

Protozoal and Parasitic Infections and the Kidney

Malaria

The World Health Organization (WHO) reported 228 million cases of malaria worldwide in 2018, 93% in Africa; 405,000 deaths were reported, 94% of which occurred in Africa [104]. Figure 14.8 shows the distribution of malaria

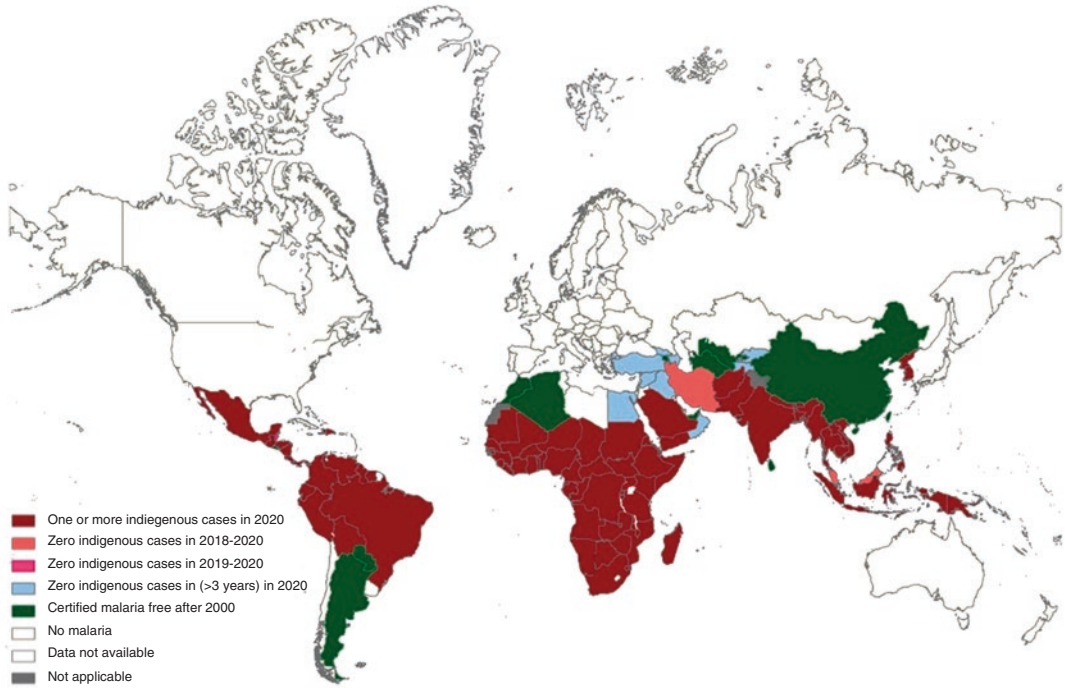

Fig. 14.8 Countries with indigenous cases in 2000 and their status by 2020: Countries with zero indigenous cases for at least three consecutive years are considered to have eliminated malaria. In 2020, the Islamic Republic of Iran and Malaysia reported zero indigenous cases for the third consecutive year, and Belize and Cabo Verde reported zero indigenous cases for the second time. China and El Salvador were certified malaria free in 2021, following 4 years of zero malaria cases. (Reproduced with permission from the World Health Organisation (WHO) [105])

worldwide [106]. The most vulnerable groups are young children, who have not yet developed immunity to malaria, and pregnant women, whose immunity has decreased with pregnancy. Malaria is transmitted by the bite of an infected *Anopheles* mosquito. There are four pathogenic species of malaria: *Plasmodium falciparum, P. vivax, P. ovale, P. malariae; P. falciparum* causes the most severe disease with heaviest parasitaemia. The clinical presentation of severe disease is dehydration with hypotension, oliguria, severe anaemia and jaundice.

Kidney Disease with Malaria

Malarial nephropathies are reported in endemic areas, such as Southeast Asia, India, and Sub-Saharan Africa [107–109]. Histologic evidence shows the presence of acute tubular necrosis, interstitial nephritis and glomerulonephritis [110–113] (Table 14.8).

Acute kidney injury (AKI) occurs in severe malaria in less than 4.8% of cases, with clinical presentation of hypotension, oliguria, severe anaemia, jaundice, and hepatosplenomegaly and a high risk of mortality (15–45%) [107–109]. Risk factors for malarial AKI include delayed diagnosis, heavy parasitaemia, volume depletion, hyperbilirubinaemia, intravascular haemolysis, kidney ischaemia, sepsis, disseminated intravascular coagulation (DIC), cytoadherence to endothelial cells, and microvascular sequestration [114]. Endothelial activation leads to the release of several cytokines, including thromboxane, catecholamines, endothelin and other inflammatory mediators, that are also implicated in the pathogenesis of malaria-associated kidney injury [114].

Immune system activation in malaria involves Th1 and Th2 responses [110]. When the Th2 response prevails (especially with infection by *P. malariae)*, complement activation occurs, with immune complex deposition leading to glomerulonephritis. When Th1 response is predominant, acute interstitial nephritis and acute glomerulonephritis occur. Renal cortical necrosis has also been described in malaria, characterizing more severe kidney injury and is generally associated with non-recovery of kidney function and development of end-stage kidney disease (ESKD) [112]. Hepatic dysfunction also contributes to kidney disease in malaria: hyperbilirubinemia can lead to cast nephropathy, and AKI, and liver disease and its complications can also cause AKI (hepato-renal syndrome (HRS)) [111, 113, 115–117]. The principal pathogenic mechanisms of kidney disease in malaria are depicted in Fig. 14.9.

Table 14.8 Kidney disease with different malaria species

Kidney disease	Malaria species
Acute kidney injury Acute tubular necrosis Acute interstitial nephritis	*P. falciparum; P. vivax; P.ovale; P.malariae* (less commonly)
Renal cortical necrosis	*P. falciparum; P. vivax (rarely)* [111, 112]
Glomerular disease	*P. falciparum; P. malariae; P. vivax* (rarely) [113]

Diagnosis

Microscopy is the gold standard and preferred option for diagnosing malaria. In nearly all cases, examination of thick and thin blood films will reveal malaria parasites. Thick films are more sensitive than thin films for detecting low levels of parasitaemia.

Rapid diagnostic tests (RDT) are useful for diagnostic purposes, especially for diagnosing malaria in patients who have recently received antimalarial treatment and in whom blood films are transiently negative for malaria parasites. Commonly targeted antigens are histidine-rich protein 2 (HRP2), which is specific for P. falciparum, and plasmodium lactate dehydrogenase (pLDH), which is present in all Plasmodium species [115, 116].

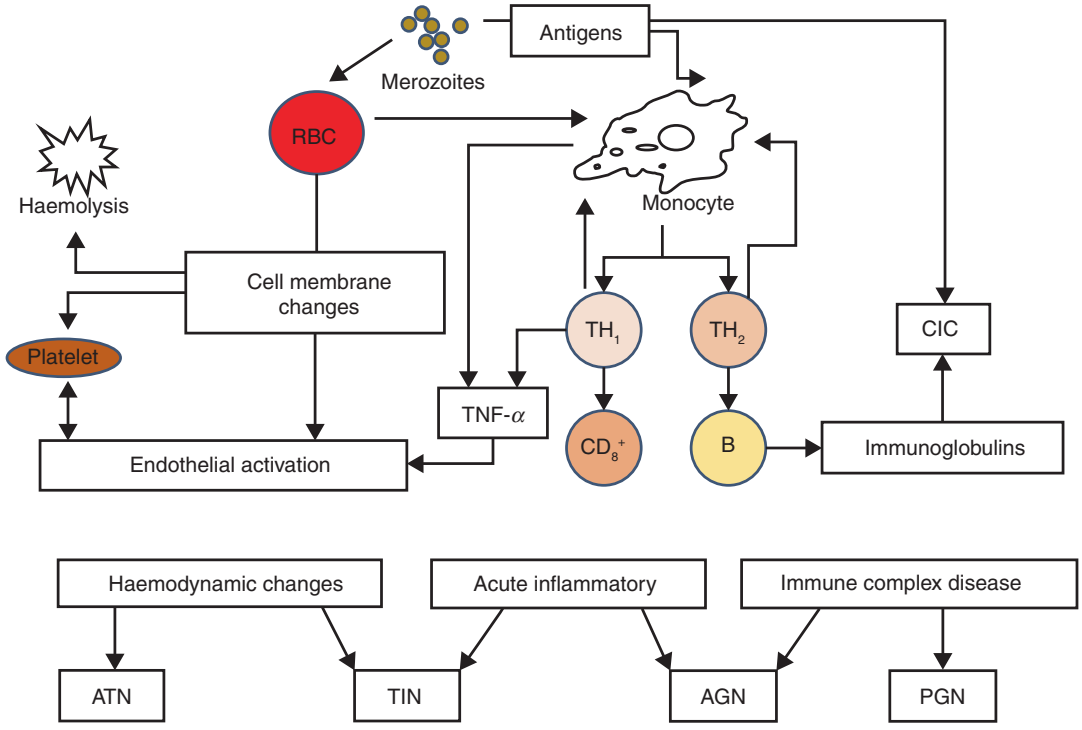

Fig. 14.9 Mechanisms of kidney disease with malaria (adapted from Barsoum RS, 1998) [110]. *ATN* acute tubular necrosis, *TIN* tululo-interstitial nephritis, *AGN* acute glomerulonephritis, *PGN* progressive glomerulonephritis, *CIC* circulating immune complexes, *RBC* red blood cell

Treatment

The control and eradication of malaria demands a multifaceted approach, including insecticide spraying and insecticide-treated bed nets.

Close monitoring with rehydration, correction of hypoglycaemia (if present) and control of any seizures are important. If the patient remains oliguric after adequate rehydration, and kidney function continues to decline, then KRT (haemofiltration or haemodialysis, and if neither is available, peritoneal dialysis) should be implemented, especially for severe disease. Haemofiltration is more efficient, and is associated with a significantly lower mortality than peritoneal dialysis. When possible, refer the patient to a dialysis unit.

The current WHO-recommended first-line treatment for the majority of malaria cases is artemisinin-based combination therapy (ACT) (Table 14.9).

Table 14.9 Treatment of severe malaria [117]

Drug	Treatment schedule
Pre-referral treatment Artesunate rectally Artesunate IMI Artemether IMI Quinine IMI	Given if delay in receiving definitive Rx for >6 h 10 mg/kg OR 2.4 mg/kg OR 3.3 mg/kg OR 20 mg/kg (10 mg/kg into each thigh)
Artesunate	2.4 mg/kg body weight (BW) IVI or IMI on admission, and then 12 hourly × 24 h (until oral intake is possible) OR
Artemether	3.2 mg/kg BW IMI on admission, then 1.6 mg/kg BW daily OR
Quinine HCl	20 mg/kg loading dose on admission, then 10 mg/kg 8 hourly as IV infusion over 2–4 h in 10 mL/kg BW isotonic fluid OR IMI in 2 sites. Duration X 24 h (minimum)
Follow-up oral Rx: Artemether + Lumefantrine Artesunate + Amodiaquine Artesunate + Mefloquine[a] Artesunate + sulfadoxine-pyrimethamine Dihydroartemisinin + Piperaquine	Full course for to be given when able to take oral medication

[a]Avoid in presence of cerebral malaria due to risk of neuropsychiatric side effects

Schistosomiasis

Approximately 240 million people worldwide, living in poor communities without potable water and inadequate sanitation, are affected by schistosomiasis, which is prevalent in tropical and sub-tropical areas of the world (Fig. 14.10) [118], with 90% living in Africa. It is estimated that more than 200,000 deaths per year are due to schistosomiasis in sub-Saharan Africa. Table 14.10 depicts the geographical distribution of the different schistosomal species [119].

Clinical Features

The incubation period for patients with acute schistosomiasis is usually 2–12 weeks; many people are asymptomatic and have subclinical disease during both acute and chronic stages of infection. Acute infection (Katayama syndrome) may present with rash, fever, headache, myalgia, and respiratory symptoms. Eosinophilia is often present with hepato- and/or splenomegaly [120].

Clinical manifestations of chronic disease result from host immune responses to schistosomal ova. *S. mansoni* and *S. japonicum* ova most commonly lodge in the blood vessels of the liver or intestine and can cause diarrhoea, constipation, and blood in the stool. Chronic inflammation can lead to bowel ulceration, hyperplasia, and polyposis; and with heavy infections, may result in liver fibrosis and portal hypertension. *S. haematobium* ova tend to lodge in the urinary tract causing dysuria and haematuria. Chronic infections may increase the risk of bladder cancer. *S. haematobium* ova deposition has also been associated with damage to the female genital tract, causing female genital schistosomiasis. Central nervous system lesions are rare and due to ectopic deposition of ova in the spinal cord (*S. mansoni* or *S. haematobium*) or brain (*S. japonicum*) forming granulomas that act as space occupying lesions [121].

Fig. 14.10 World-wide Prevalence of Schistosomiasis [118]. (Reproduced with permission from the authors of Ismail et al., 2016 [118])

Table 14.10 Geographical distribution of the different types of Schistosomes [119]

	Species	Geographical distribution
Intestinal schistosomiasis	*Schistosoma mansoni*	Africa, the Middle East, the Caribbean, Brazil, Venezuela and Suriname
	Schistosoma japonicum	China, Indonesia, the Philippines
	Schistosoma mekongi	Several districts of Cambodia and the Lao People's Democratic Republic
	Schistosoma guineensis and related *S. intercalatum*	Rain forest areas of central Africa
Urogenital schistosomiasis	*Schistosoma haematobium*	Africa, the Middle East

Kidney Disease

Glomerular disease occurs in 5–15% of those with *S. mansoni* infection [122], and has been described in 10–12% of autopsy studies [123]; proteinuria occurs in 20% of *S. mansoni*-infected patients [124]. Glomerular injury is due to the deposition of schistosomal antigens in the glomerulus and subsequent immune response [121]. The histopathological patterns described are mesangial proliferative GN, membranoproliferative GN, FSGS, proliferative GN and amyloidosis [122].

S. haematobium infections present with haematuria, with granuloma formation; if untreated, the disease may progress to bladder fibrosis, calcification, vesico-ureteric reflux and hydronephrosis, and CKD [120]; the risk of bladder cancer is increased. Rarely, glomerulopathy has been described with *S. haematobium*, with a case report of membranoproliferative GN [123].

Figure 14.11 describes the timelines associated with the pathogenesis and the different disease manifestations of schistosomiasis [124].

Diagnosis

Schistosomiasis is diagnosed by the detection of ova in stool (*S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum*) or urine (*S. haematobium)* specimens. Antibodies and/or antigens detected in blood or urine samples are also indicative of infection [119, 120].

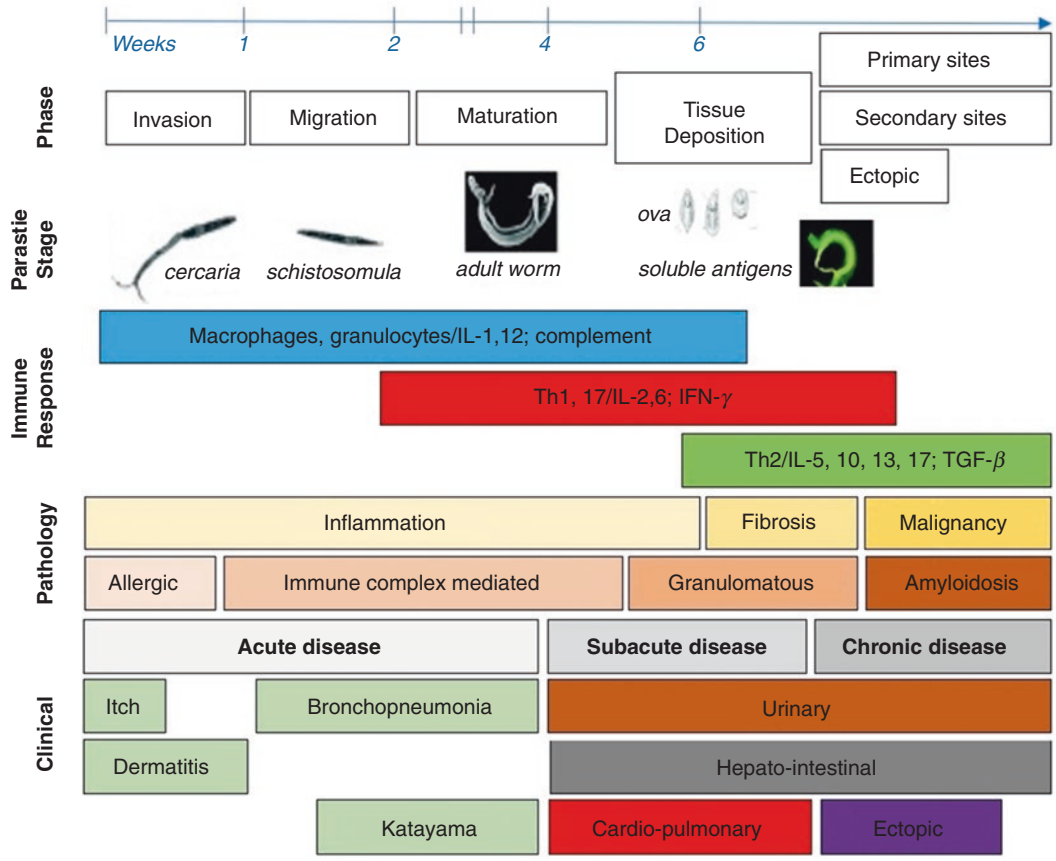

Fig. 14.11 Timelines, Clinical features and Pathogenesis of Schistosomal Disease (adapted from Barsoum R et al., 2013 [124])

Table 14.11 Treatment schedule for Schistosomiasis by *Schistosoma* species infection

Schistosoma species infection	Praziquantel dose and duration
S. mansoni, S. haematobium, S. intercalatum	40 mg/kg per day orally in two divided doses for one day
S. japonicum, S. mekongi	60 mg/kg per day orally in three divided doses for one day

Treatment

Infections with all major *Schistosoma* species can be treated with praziquantel (Table 14.11). Although a single course of treatment is usually curative, repeat treatment may be needed after 2 to 4 weeks to increase effectiveness [119].

Prevention and Control

The control of schistosomiasis is based on large-scale treatment of at-risk population groups, access to safe water, improved sanitation, education, and snail control. Preventive measures include avoiding contact with freshwater in disease-endemic countries.

The WHO strategy for schistosomiasis control focuses on reducing disease by periodic, targeted treatment with praziquantel of all at-risk population groups [119].

Fungal Infections and Kidney Disease

Fungal infections occur more commonly in hospitalized or immunocompromised patients; Table 14.12 outlines the major risk factors for fungal infections of the kidney. Most common organisms are Candida species [125]; less common fungi are filamentous fungi (Mucor, Aspergillus, Penicillium); and rare are endemic fungi (Blastomycosis, Histoplasmosis, Coccidioidomycosis). Patients who are symptomatic usually have urinary tract obstruction from masses of fungal elements (fungal balls). Angio-invasion by fungi may lead to numerous micro-abscesses in the kidney, and extensive kidney infarcts, leading to kidney dysfunction. Treatment with systemic antifungal agents, and surgical removal of the obstructing mass is usually required [126]. In extensive disease, mortality remains very high, especially with angio-invasive fungal infection with mucormycosis and aspergillus infections [127].

Table 14.12 Major risk factors for fungal infections of the kidney

Major risk factors for fungal infections of the kidney
Older age
Female gender
Prolonged antibiotic use
Indwelling catheter
Prior surgical procedures
Mechanical ventilation
Parenteral nutrition
Diabetes mellitus
Immunocompromised state (including post kidney transplantation)

Conclusions

Kidney and urinary tract infections are associated with significant morbidity—and amongst vulnerable groups, mortality. The first clinical case describes a bacterial infection with *E. Coli*, and illustrates how clinical presentations with urinary tract infection may be unusual, but with appropriate clinical awareness, affected patients can be commenced on appropriate antibiotics early, and hence offered the best chance of a full recovery. The second clinical scenario illustrates the reversible nature of infection-related immune-mediated glomerulonephritis, which may present in a young female who is very unwell, confused and dialysis dependent.

Questions

1. A 55 year old man presented to the emergency room with fever, non-productive cough, anosmia, muscle aches and fatigue for one day and sore throat for 3 days. He had been to his local pub 5 days previously. His

temperature was 38.3 °C, BP 124/76, respiratory rate 28/min and oxygen saturation 88%. Chest radiograph was suggestive of bilateral lower lobe interstitial pneumonitis. Laboratory results revealed haemoglobin 13.3 g/dL; white cell count 4.1×10^9/L; lymphocyte count 1.3×10^9/L; blood glucose 12.2 mmol/L; serum creatinine 98 μmol/L; CRP 185 mg/L. Three days after admission he was breathless and transferred to ITU, his creatinine increased to 210 μmol/L.

What is the most likely cause of his illness?

A. COVID-19
B. Cytomegalovirus infection
C. Staphylococcus infection
D. Pneumococcus infection
E. Malaria

Answer: A

A nasal swab PCR confirmed the diagnosis of COVID-19. He was admitted to the intensive care unit and commenced on intravenous fluids, high flow oxygen via a nasal cannula, enoxaparin 20 mg subcutaneously, dexamethasone 6 mg daily intravenously and insulin adjusted according to glucometer readings. He was transferred out of ICU after 5 days and continued to improve in hospital.

2. A 30 year old black woman, recipient of a deceased donor kidney transplant 3 months previously, was noted to have a decline in her baseline kidney function at a clinic visit. She had received antithymocyte globulin, high dose steroid induction therapy and was being maintained on tacrolimus, mycophenolate mofetil (MMF) and prednisolone. She had been noted to be CMV IgG positive while on dialysis. Her BP was130/60 mmHg, pulse 78/min and temperature 39 °C. Laboratory tests: haemoglobin 11.8 g/dL; WCC 3.1×10^9/L; platelet count 130,000; serum creatinine 180 μmol/L from a previous baseline of 110 μmol/L. Urine examination revealed 50 red cells/HPF and proteinuria of 0.5 g/day. Tacrolimus levels were between 5 and 15 ng/mL. She underwent a kidney biopsy.

   Histology of the allograft biopsy showed a peritubular mononuclear interstitial infiltrate; some tubular cells had intranuclear inclusions.

   What is the most likely diagnosis?

   A. Acute cellular rejection
   B. Acute antibody mediated rejection
   C. BK virus infection
   D. Cytomegalovirus infection
   E. Tacrolimus toxicity

   Answer: D

   CMV viral load was 15,000 copies/mL. She was treated with intravenous ganciclovir 5 mg/kg every 12 h for 14 days, and thereafter maintained on valganciclovir 900 mg daily for 30 days. MMF was discontinued, tacrolimus dose was optimized according to blood levels, and she continued with low dose prednisolone. Her serum creatinine stabilized at 125 μmol/L.

3. An 18-year old boy, recipient of a second (deceased donor) kidney transplant was noted to have an asymptomatic rise in his serum creatinine during a routine clinic visit 12 months after transplantation. He had received antithymocyte globulin, high dose steroid induction therapy and was being maintained on tacrolimus, mycophenolate mofetil (MMF) and prednisolone. He had been noted to be CMV IgG positive previously. He was noted to have haemoglobin 12.8 g/dL; WCC 5.1×10^9/L; platelet count 230,000; serum creatinine 220 μmol/L from a previous baseline of 120 μmol/L. Urine cytology showed epithelial cells with viral inclusions ‘decoy cells’, Allograft biopsy showed mononuclear interstitial inflammation, and some degree of tubulitis with basophilic changes of the tubular epithelium.

   What is the most likely diagnosis?

   A. Acute cellular rejection
   B. Acute antibody mediated rejection
   C. BK virus infection
   D. Cytomegalovirus infection
   E. Tacrolimus toxicity

   Answer: C

   He had a urine BK load of 11^7 copies/mL and a serum BK viral load of 10^5 copies/mL. His MMF dose was halved, and tacrolimus trough levels lowered and he was treated

with leflunomide 100 mg daily for 5 days and 40 mg daily thereafter until the virus was cleared. His kidney function gradually stabilized to around his baseline levels and surveillance for BKV is carried out on a monthly basis.

4. A 45 year old black man was recently diagnosed with HIV infection and referred to a Renal Clinic with proteinuria and renal dysfunction. He had minimal ankle oedema, BP 126/82 and had 3 g proteinuria/day. His serum albumin was 25 g/L, serum cholesterol 4.1 mmol/L, serum creatinine 188 μmol/L, eGFR 42.1 mL/min/1.73 m^2, CD4 count 180 cells/mL, viral load 125,000 copies/mL. He underwent a kidney biopsy.

   What is the most likely biopsy diagnosis?

   A. Crescentic glomerulonephritis
   B. Focal segmental glomerulonephritis
   C. Membranous glomerulonephritis
   D. Membranoproliferative glomerulonephritis
   E. Minimal change disease

   Answer: B

   His kidney biopsy showed typical HIV associated nephropathy, with glomerular collapse, microcystic tubular dilatation and interstitial inflammation. He was commenced on Losartan 50 mg daily, and Abacavir 300 mg BD, Lamuvidine (3TC) 150 mg daily and Dolutegravir 50 mg daily. Avoid fixed dose combinations if GFR < 50 mL/min, and tenofovir if possible. His APOL1 genotype was not available.

5. A 25 year old man was admitted to the emergency room with a fever of 39.1 °C, and dehydration. He had been on a beach vacation in Mozambique 2 weeks previously. He was noted to have tachycardia of 100/min, BP 96/60 and was pale and had a 2 cm splenomegaly. His haemoglobin was 10.1 g/dL; white cell count 4.1 × 10^9/L; platelets 92,000; serum bilirubin 35 mmol/L; blood urea 32 mmol/L; serum creatinine 220 μmol/L.

   What is the most likely cause of his acute kidney injury?

   A. Cytomegalovirus infection
   B. Epstein barr virus infection
   C. Malaria
   D. Pneumococcal infection
   E. Staphylococcus infection

   Answer: C

   A thin smear revealed the presence of tropozoites of P falciparum. He was commenced on intravenous fluids and therapy with artesunate 2.4 mg/kg intravenously immediately and 12 hourly for 24 h and thereafter switched to oral treatment with artemether-lumefantrine for 3 days. A blood smear at 72 h demonstrated that the parasitaemia had been eradicated and he made a a full recovery.

6. A 45 year old man, a visitor from Egypt, was hospitalized with abdominal distension. He had been an agricultural worker. He was noted to have hepatosplenomegly. Investigations showed dipstick proteinuria of 3+, and was measured to be 2.9 g/24 h; serum albumin 35 g/L; serum globulins 50 g/L; haemoglobin was 10.8 g/dL; white cell count 4.1 × 10^9/L; platelets 112,000; serum bilirubin 10 mmol/L; blood urea 5 mmol/L; serum creatinine 88 μmol/L. Ultrasound of the liver was suggestive of hepatic fibrosis, and was confirmed by fibroscan. A kidney biopsy showed membranoproliferative glomerulonephritis.

   What is the cause of the renal disease?

   A. Cytomegalovirus infection
   B. Hepatitis B infection
   C. HIV infection
   D. Malaria
   E. Schistosomiasis

   Answer: E

   A stool specimen showed the presence of schistosoma mansoni. He was treated with praziquantel and advised to avoid future schistosomal infection, and to return to his physician for review.

7. A 25 year old forest worker in the Democratic Republic of the Congo presented to the Emergency Department with 3 day history of headache, fever, shivering at night, muscle ache and joint pains. The headache was worst behind the eyes and he also mentioned shivering at night. His temperature was 40.0 °C

with a BP of 100/60 and regular tachycardia of 120/min. By Day 4 he had developed a maculo-papular rash with patches of purpura. Haemoglobin 13.0 g/dL, WBC 4.0 × 10^9/L, platelets 80 × 10^9/L [normal: 150–400]. Creatinine 350 μmol/L with urea 40 mmol/L, eGFR 24 mL/min/1.73 m^2. There was proteinuria 0.6 g/L and RBC 50–100/μL. Renal biopsy was not considered as it was felt that it would not influence treatment; furthermore it would add an unnecessary hazard for someone already at risk of bleeding.

What is the most likely diagnosis?

A. COVID 19 infection
B. Dengue fever
C. Ebola virus infection
D. Malaria
E. Tuberculosis infection

Answer: B

He was diagnosed with Dengue fever and managed with supportive treatment and scrupulous attention to clinical signs, pulse, blood pressure and urine output replacing fluid as necessary but avoiding overload. There is unfortunately no specific treatment for dengue virus and as yet no vaccine.

8. An 18 year-old female presented with history of fever for 2 weeks, and the passage of brown urine for 6 days, generalized body swelling for 5 days followed by reduced urine output and breathlessness for 2 days. She had a seizure episode a few hours before presentation. She had noted skin infections 3 weeks preceding the above symptoms. On presentation, she had impaired consciousness (GCS 8/15) but recovered within a few hours. She was pale, with bilateral pitting leg oedema temperature of 37.8 °C, respiratory rate 38 breaths/min, pulse 110 bpm and BP 160/110 mmHg. Urinalysis showed blood, protein, and microscopy revealed red cell casts. Her blood tests showed sodium: 122 mmol/L, potassium: 5.6 mmol/L, HCO_3: 12.4 mmol/L, chloride: 84.4, iCa: 1.01, BUN: 63.3 mmol/L, creatinine: 884 μmol/L, haemoglobin: 8.3 g/dL, leukocytosis with neutrophila of 78%.

   What is the most likeley investigation which will help with diagnosis?

   A. ASO titre
   B. ANCA
   C. Hepatitis B serology
   D. Kidney biopsy
   E. Serum immunoglobulin

   Answer: A

   Her ESR was 125 mm/hr and qualitative ASO titre**:** elevated/positive

9. An 18 year-old female presented with history of fever for 2 weeks, red-brown coloured urine for 6 days, generalized body swelling for 5 days followed by reduced urine output and breathlessness for 2 days. She had a seizure episode a few hours before presentation. She had noted skin infections 3 weeks preceding the above symptoms. On presentation, she had impaired consciousness (GCS 8/15) but recovered within a few hours. She was pale, with bilateral pitting leg oedema temperature of 37.8 °C, respiratory rate 38 breaths/min, pulse 110 bpm and BP 160/110 mmHg. Urinalysis showed blood, protein, and microscopy revealed red cell casts. Her blood tests showed sodium: 122 mmol/L, potassium: 5.6 mmol/L, HCO_3: 12.4 mmol/L, chloride: 84.4, iCa: 1.01, BUN: 63.3 mmol/L, creatinine: 884 μmol/L, haemoglobin: 8.3 g/dL, leukocytosis with neutrophila of 78%.

   What is the most likely diagnosis?

   A. Haemolytic uraemic syndrome
   B. IgA nephritis
   C. Lupus nephritis
   D. Post infectious glomerulonephritis
   E. Polyarteritis nodosa

   Answer: D

   Her ESR was 125 mm/hr and qualitative ASO titre**:** elevated/positive

10. A 42 year old rural drainage engineer, living in Sao Paulo state in southern Brazil, presented to the Dermatology clinic giving a history of intermittent skin rash sometimes associated with a change in pigmentation. He was found to have heavy proteinuria and referred to the nephrologist. In recent months he had been feeling more tired than usual. He

had a pale complexion. There was mild oedema of the ankles. Temperature: 36.5 °C, Haemoglobin 100 g/L, sodium 140 mmol/L, Potassium 5.3 mmol/L, bicarbonate 22 mmol/L, creatinine 216 μmol/L, albumin 23 g/L. Urine protein amounted to 10.5 g/24 h. An MSU revealed neither cells nor blood or glucose; the urine was sterile on culture. A repeat of the investigations a week later gave similar results.

What is the most likely diagnosis?

A. Leptospirosis
B. Systemic lupus erythematosus
C. Nephropathy of tuberculoid leprosy
D. Amyloidosis secondary to lepromatous leprosy
E. Falciparum malaria

Answer: D Amyloidosis secondary to lepromatous leprosy

A.	Leptospirosis	Incorrect	Lack of fever, and no active urinary sediment
B.	Systemic lupus erythematosus	Incorrect	No joint pain, no fever, no significant urinary sediment
C.	Nephropathy of tuberculoid leprosy	Incorrect	Nephrotic syndrome not common in the tuberculoid form of leprosy
D.	Amyloidosis secondary to lepromatous leprosy with nephrotic syndrome	Correct	Frequency of amyloidosis in leprosy types: lepromatous [36%], tuberculoid and borderline [5%]. The nephrotic syndrome is a consequence of the amyloidosis.
E.	Falciparum malaria	Incorrect	No fever or other evidence of malaria

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