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13.1 Introduction

Tropical renal diseases are infectious or toxin-mediated diseases that affect the kidney and occur predominantly in tropical and subtropical regions. The pathogenesis of renal complications in tropical conditions is multifactorial. Factors which are unique to the tropics and which may play a role in specific renal outcomes include the distinct type of prevalent pathogens, vegetation and disease vectors, the increased population density, high prevalence of malnutrition, and the use of local alternative medications. With increasing global travel, tropical diseases are no longer confined only to the tropics but are increasingly seen in nontropical areas as well.

13.2 Classification

1. Infections

- (a) ***Parasitic infections***
 - Malaria
 - Schistosomiasis
 - Filariasis
 - Visceral leishmaniasis
- (b) ***Bacterial infections***
 - Leptospirosis
 - Rickettsial infections

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Enteric pathogens
Renal and genitourinary tuberculosis

(c) **Viral pathogens**

Viral hemorrhagic fever (dengue, hantavirus, yellow fever virus)

2. **Toxic injuries**

Snakebite nephropathy
Scorpion bites
Natural medicines

13.3 Malaria

Introduction: Malaria is caused by the protozoan *Plasmodium* and is a huge public health burden globally, particularly in children. The overall incidence of malarial nephropathy is low at 2–5 % among those living in endemic areas; however, up to 30 % of nonimmune visitors with malaria develop renal complications (Fig. 13.1).

Transmission: The parasite is transmitted by the Anopheles mosquito. Of the 4 plasmodium species, nephropathy is seen most frequently with *P. falciparum* and rarely with *P. vivax* and *P. ovale*. “Quartan malarial nephropathy” associated with *P. malariae* infections in children causing nephrotic syndrome and chronic renal failure observed in the 1970s in Africa has become extremely rare with no recent reports in the literature (Fig. 13.2).

Clinical Features: The classic features of malaria are spiking fevers with rigors. Other features are malaise, headache, nausea, and hypotension. Chronic anemia and splenomegaly are observed in endemic areas. Severe infection may include acute kidney injury, coma and seizures, pulmonary edema, acute respiratory distress syndrome (ARDS), jaundice, shock, and disseminated intravascular coagulation.

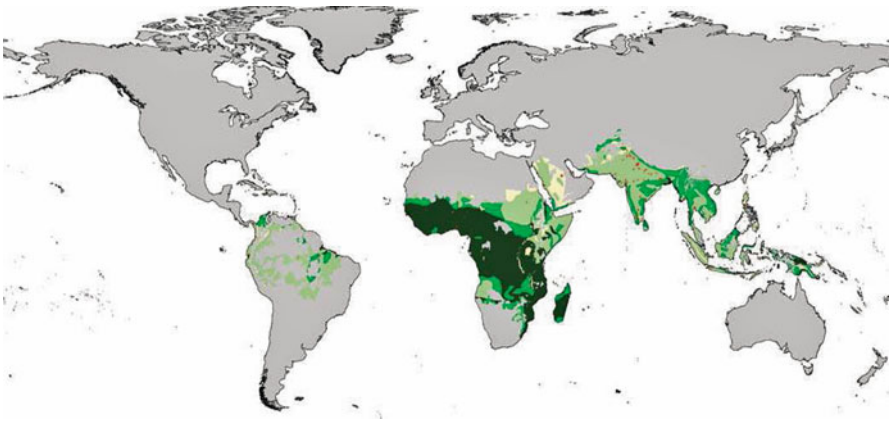


Fig. 13.1 Global distribution of *Plasmodium falciparum*. Light green, childhood infection prevalence is <10 %; medium green, prevalence 11–50 %; dark green, prevalence >50 % (Source: WHO)

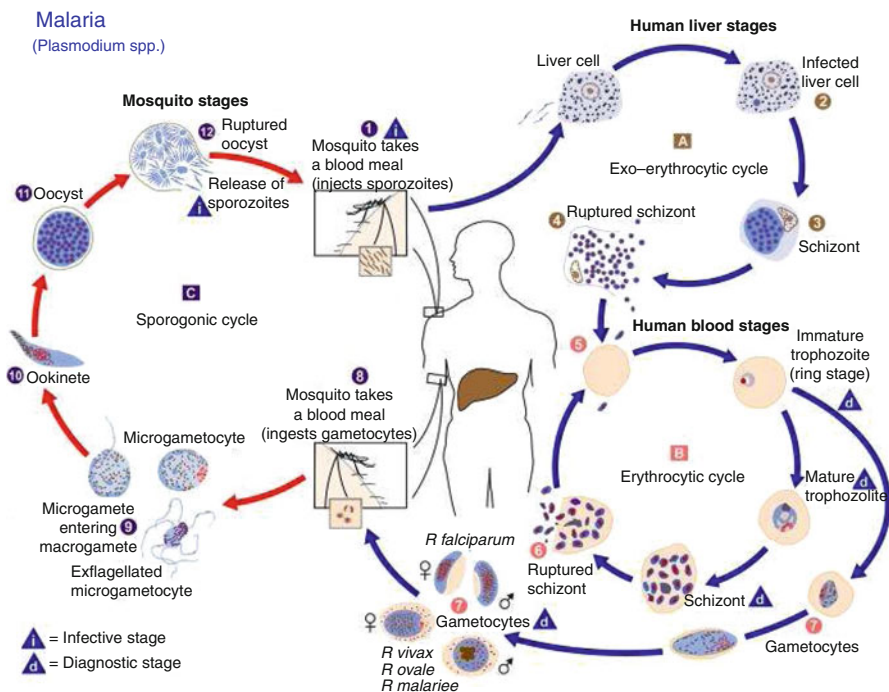


Fig. 13.2 Life cycle of *Plasmodium* species (Source: Public Health Image Library, # 3405)

Renal Involvement: Transient proteinuria in uncomplicated malaria lasts usually less than 1 week after initiation of antimalarial therapy and can be observed in 30 %.

Malarial acute kidney injury (MAKI) is defined as an abrupt reduction (<48 h) in renal function or serum creatinine >3 mg/dl in a child with falciparum malaria (WHO criteria). It is seen in about a third of those with cerebral malaria, and is usually oliguric, and accompanied by hyperkalemia and acidosis.

The causes of MAKI in malaria may be multifactorial:

1. Shock leading to hypotension and reduced renal perfusion.
2. Intravascular hemolysis and hemoglobinuria (black water fever) often associated with use of antimalarial drugs such as quinine, halofantrine, or mefloquine.
3. Disseminated intravascular coagulation (DIC) and rhabdomyolysis are rare causes.
4. Antimalarial drugs may precipitate hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals resulting in hemoglobinuria and AKI.

Renal Pathophysiology: The predominant lesions are acute tubular necrosis, mild proliferative glomerulopathy, and varying degrees of interstitial nephritis. *P. falciparum* is associated with alteration in red cell surface structure resulting in increased cytoadherence to vascular endothelial cells and red cell sequestration, which in turn interferes with microcirculatory flow with subsequent multiorgan involvement. In severe hemolysis, vacuolization of proximal tubular cells and hemoglobin deposition in tubules are seen. Immunofluorescence shows mesangial C3 and IgM

deposition. EM shows subendothelial and mesangial electron-dense deposits with granular, fibrillar, and amorphous material. Immune complexes of malarial antigen can be present in the glomerular basement membrane.

Diagnosis: Blood smear examination using thick and thin smears stained with Giemsa stain revealing the presence of asexual forms of *P. falciparum* is diagnostic. Staining with the fluorescent dye acridine orange increases sensitivity. Rapid diagnostic tests (RDTs) that detect the presence of *P. falciparum*-specific antigens are also in use.

Treatment: The main principles of treatment are (1) prompt use of combination anti-malarial drugs (quinine or artemisinin derivatives; no dosage adjustment is required in the presence of renal dysfunction unless quinine needs to be given as a parenteral dose beyond 48 h; in this situation, two-thirds dose can be administered), (2) maintenance of fluid and electrolyte balance, (3) renal replacement therapy at the earliest indication, (4) treatment of associations and infections, and (5) careful use of concomitant drugs (avoid nephrotoxic drugs such as aminoglycosides, NSAIDs, and ACE inhibitors). The use of diuretics should be avoided. In severe disease, partial exchange transfusion has been used when the parasite index is >20 % in order to remove infected red blood cells from circulation and reduce parasite burden and also alleviate microcirculatory obstruction, although a clear consensus on indications has not yet been achieved.

Prognosis: Malarial AKI may resolve completely and is not usually associated with chronic renal disease or hypertension. The overall mortality from malarial AKI varies between 15 and 50 %. Survival rates are better when hemodialysis rather than peritoneal dialysis was instituted early.

13.4 Schistosomiasis

Introduction: Schistosomiasis is a highly prevalent helminthic infection, and human pathogenic species include *Schistosoma haematobium* (African subcontinent) and *Schistosoma mansoni* (Latin America) which are associated with renal and bladder involvement.

Transmission: Infection is acquired by contact with freshwater snails, which are the intermediate hosts. The infective agent is the cercaria which penetrates the skin and gains access to the bloodstream and reaches the portal and perivesical venous plexus via lymphatics where it rapidly grows to its adult bisexual form.

13.4.1 *Schistosoma haematobium*

Natural History: For *S. haematobium*, the female lays eggs into the submucosa of the bladder from where they are shed by the urine. The ova cause hypersensitivity reaction in the bladder leading to pseudotubercle formation, fibrosis, bladder outlet obstruction, and cystitis and predispose to squamous cell carcinoma of the bladder.

Renal Involvement: Renal clinical symptoms of *S. haematobium* infections are painful, terminal hematuria; increased frequency; and dysuria.

Renal Pathophysiology: Urine analysis shows RBCs, parasite eggs, and occasionally eosinophiluria (refer to Fig. 13.3). Pyuria and bacteriuria are seen with secondary

Fig. 13.3 Urine microscopy shows schistosoma ova with terminal spines (Source: CDC, Atlanta, USA)



bacterial infection. Functional consequences depend on extent of fibrosis and include partial obstruction at the lower ureteral ends, bladder neck obstruction, impaired detrusor contractility, vesicoureteral reflux, and hydronephrosis. Chronic infection can predispose towards developing squamous cell carcinoma of the bladder.

13.4.2 *Schistosoma mansoni*

Natural History: *S. mansoni* infects the portal venous plexus and causes colorectal disease and hepatic fibrosis.

Renal Involvement: Nephrotic edema and hypertension are seen in typical hepatosplenic schistosomiasis. Glomerulonephritis may be due to immune-mediated glomerular injury and may present with immune complex deposits in the kidney. Clinical manifestations may include proteinuria, sometimes nephrotic range, edema, and hypertension. Biopsy may show (i) exudative glomerulonephritis, (ii) mesangiocapillary glomerulonephritis, (iii) focal segmental sclerosis, and (iv) renal amyloidosis. IF may show IgG and IgA deposits.

Diagnosis: The gold standard of diagnosis is the demonstration of ova in urinary sediment (*S. haematobium*) or stool (*S. mansoni* and *S. japonicum*).

Treatment: Treatment is praziquantel 40 mg/kg/day in two divided doses for 1 day.

13.5 Filariasis

Introduction: Lymphatic filariasis is caused by the three different types of nematodes: *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*. For global distribution of filariasis, refer to Fig. 13.4.

Transmission: The disease is transmitted by different types of mosquitoes. The female mosquito releases microfilaria into the bloodstream. Infective larvae migrate

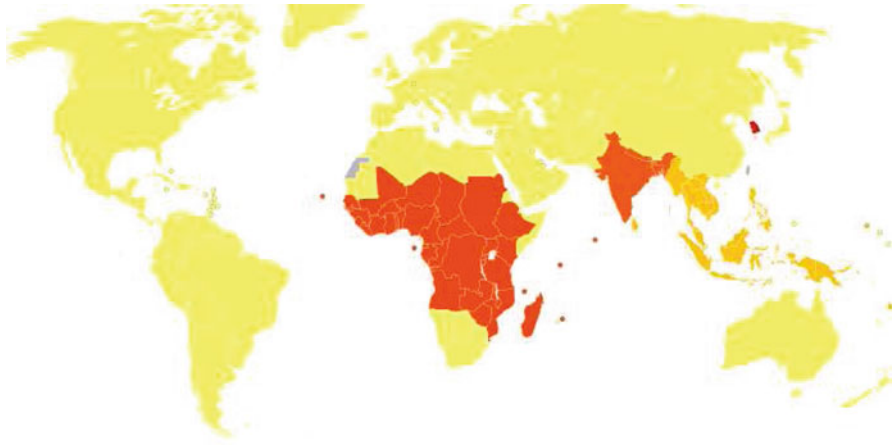


Fig. 13.4 Global distribution of filariasis (Source: World Health Organization 2002)

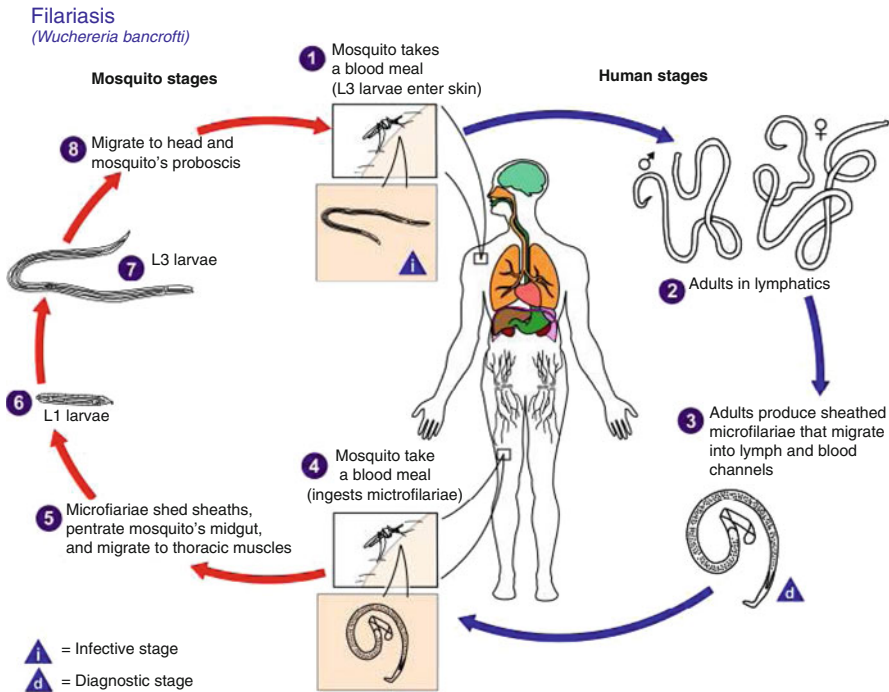


Fig. 13.5 Life cycle of *Wuchereria bancrofti* (Source: Public Health Image Library, #3425)

into the lymphatics where they slowly mature to adult worms, mate, and may reside for decades. Refer to Fig. 13.5 for life cycle of *Wuchereria bancrofti*.

Clinical Features: The disease ranges from asymptomatic subclinical infection to acute manifestations such as adenolymphangitis, filarial fever, and tropical pulmonary

eosinophilia and chronic manifestations such as lymphedema (elephantiasis), secondary infections, and renal involvement. Eosinophilia is typically found in all cases.

Renal Involvement: Microscopic hematuria and proteinuria, possibly immune complex glomerulonephritis. Chyluria occurs in bancroftian filariasis when the intestinal lymphatics drain into the renal pelvis, leading fat and protein losses through the urine and causing secondary nutritional deficiencies.

Renal Pathophysiology: Histology shows diffuse mesangial proliferative glomerulonephritis with C3 depositions. Eosinophils and microfilaria may be seen in glomerular capillaries.

Diagnosis: The standard for diagnosis is microscopic detection of microfilariae on a thick blood film. Filarial antigen assays are also available.

Treatment: Diethylcarbamazine (DEC) is the drug of choice and is effective against both microfilaria and adult filarial worms. The earlier recommended dose of this drug was 6 mg/kg given daily for 12 days. Recent studies have shown that a single dose of DEC 6 mg/kg is as effective as the above standard regimen. Other treatment options are ivermectin and albendazole. Annual treatment in endemic areas has been shown to decrease prevalence. Management of chyluria may require special low-fat, high-protein diet with supplementation of middle-chain fatty acids.

13.6 Onchocerciasis

General: Also known as river blindness, this parasitic disease is found in sub-Saharan Africa and sometimes in Central and South America and is caused by the roundworm, *Onchocerca volvulus*. Humans acquire onchocerciasis through the bite of *Simulium* black flies. Skin involvement is common and consists of intense pruritus and inflammation resulting in papules, plaques, hyperpigmentation, and widespread lichenified onchodermatitis. Ocular involvement is also common, often leading to blindness.

Renal Involvement: *Onchocerca volvulus* is associated with higher incidence of proteinuria and nephrotic syndrome in hyperendemic regions in Africa. Histology can show different types of glomerulonephritis (minimal change, mesangioproliferative, chronic sclerosing GN). Onchocercal antigens as well as IgM, IgG, and C3 can be detected on IF. Treatment with diethylcarbamazine may help to resolve early glomerular lesions but usually fails to treat renal lesions once nephrotic syndrome is manifested.

13.7 Visceral Leishmaniasis (Kala-azar)

Introduction: This zoonosis is caused by *Leishmania* species, obligate intracellular parasites of mononuclear phagocytes. Three species, *L. donovani* (Asia and East Africa), *L. chagasi* (South America), and *L. infantum* (Mediterranean region), are responsible for the “visceral” manifestations.

Transmission: The vector is the female phlebotomine sand fly, and there are several mammalian hosts including canines, rodents, and man. The incubation period ranges from 2 to 6 months.

Clinical Features: A cutaneous ulcer may develop at the site of the primary bite. Typical manifestations are fever, anorexia, weight loss, massive splenomegaly, and hepatomegaly. Hematological abnormalities such as anemia, leukopenia, and thrombocytopenia are also seen.

Renal Involvement: May occur in 50 % of those with visceral leishmaniasis and manifests as proteinuria, microscopic hematuria, or pyuria. AKI and acute interstitial nephritis have also been reported. In addition, the common modality of treatment, antimony compounds, may be associated with renal dysfunction.

Renal Pathophysiology: Mesangial proliferative GN or a focal proliferative GN, or a generalized interstitial nephritis with interstitial edema, and focal tubular degeneration. Immunofluorescence may show deposition of IgG, IgM, and C3 within the glomeruli. Electron-dense deposits in the basement membrane and mesangium may be seen through EM.

Diagnosis: Direct visualization of amastigote forms of the parasite in Giemsa- or Wright-stained tissue specimens leads to definitive diagnosis. Serological tests are not widely available.

Treatment: Amphotericin B is the main treatment. Pentavalent antimonial agents such as sodium stibogluconate were used earlier but are associated with severe toxicity, as well as high drug resistance in India.

Prognosis: Untreated visceral leishmaniasis is nearly always fatal. Renal disease is mild and typically resolves after treatment.

13.8 Leptospirosis

Introduction: Leptospirosis is a zoonosis with a high prevalence in tropical areas and is caused by a filamentous spirochaete belonging to the genus *Leptospira*. *Leptospira interrogans* is the only human pathogenic strain. Disease occurs throughout the year, with an increase in incidence seen during the monsoon season, or after natural disasters such as floods or hurricanes.

Transmission: The common vectors for this infection are wild and domesticated mammals such as rodents, dogs, pigs, cattle, horses, and others. The pathogen can survive for long periods in renal tubules of infected asymptomatic animals and up to months in untreated water. Human infection occurs incidently through contact with water or soil contaminated by urine of infected animals. The usual portals of entry are abraded skin and exposed mucosae.

Natural History: Disease manifestation varies from subclinical infection to self-limited anicteric febrile illness to severe, potentially fatal disease. After an incubation period of 2–26 days, the majority of those infected present with a mild anicteric illness. Only 10 % become severely ill with jaundice and multiorgan involvement in Weil's disease which is associated with a mortality of 50 %.

Clinical Features: The usual illness follows a biphasic course. The leptospiremic phase is characterized by high fever with chills, headache, myalgias, skin rashes, nausea, vomiting, and conjunctival effusion for 3–9 days, followed by 2 days of defervescence. Subsequently, the immune phase sets in, featuring recurrence of fever, aseptic meningitis, and uveitis. The severe form or Weil's disease is constituted by renal insufficiency, hepatic dysfunction, thrombocytopenia, hemorrhagic manifestations, myocarditis, and high mortality.

Renal Involvement: Renal involvement is almost universal in leptospirosis and includes proteinuria, pyuria, hematuria, and hyaline and granular casts even in absence of renal dysfunction. The incidence of leptospirosis-induced acute kidney injury varies from 10 to 60 % of infected patients and is typically associated with polyuria and hypokalemia with increased fractional excretion of potassium. Hypomagnesemia and hypophosphatemia may also be present. Hypotension is also found in several cases and is often unresponsive to volume expansion and inotropic support.

Renal Pathophysiology: Leptospiral nephropathy is characterized by interstitial nephritis and tubular damage with relative glomerular sparing. Histopathological features include tubular necrosis and tubulointerstitial inflammation with infiltration by lymphocytes, plasma cells, macrophages, and polymorphonuclear leukocytes. In addition, glomerular mesangial hyperplasia with C3 and IgM deposition and, occasionally, glomerular infiltration of inflammatory cells can be found.

Diagnosis: Diagnosis can be made by serologic testing using IgM-specific dot enzyme-linked immunosorbent assay or microscopic agglutination test (MAT). Direct smear of lesions using dark field microscopy to demonstrate the organisms can be used in some cases. Culture of organisms from blood or urine is less frequently done.

Treatment: Treatment should be instituted as soon as the diagnosis is suspected as it shortens the clinical course and severity of infection. Penicillin G (200,000–250,000 U/kg/day in divided doses every 4–6 h) is recommended for serious infection. Less serious infections can be treated with doxycycline (2 mg/kg/day divided into two doses for children >8 years of age) or amoxicillin (50 g/kg/day in three divided doses). Duration of treatment is 7–14 days. Supportive management includes correction of hypotension and fluid and electrolyte imbalance. Dialysis may be necessary in severe AKI.

Prognosis: Poor prognostic factors include older age, hypotension, pulmonary complications, hyperbilirubinemia, and hyperkalemia. Children have better outcomes compared to adults. Survivors may have a residual defect in tubular concentrating ability.

13.9 Rickettsial Infections

Introduction: Rickettsioses are important emerging infections caused by infection with a family of microorganisms that have both viral and bacterial features.

Transmission: Arthropods such as ticks, lice, and mites are the common vectors, and infection occurs when humans get bitten by these infected vectors.

Clinical Features: Infected individuals present with an acute febrile illness, erythematous rashes, and widespread vasculitis.

Renal Involvement: Subclinical renal involvement secondary to vasculitis probably occurs in many of the rickettsial diseases. In certain rickettsiosis, Rocky Mountain spotted fever (*Rickettsia rickettsii*), tick typhus (*Rickettsia conorii*), and Q fever (*Coxiella burnetii*), clinical renal involvement may be more common and may manifest as elevated creatinine and urea along with metabolic acidosis.

Renal Pathophysiology: Rickettsia multiply in endothelial cells causing focal areas of endothelial cell proliferation, perivascular mononuclear cell infiltration, and thrombosis. Renal biopsy shows interstitial vasculitis and acute tubular necrosis.

Diagnosis: Serology is the mainstay of diagnosis and is based on detection of IgM antibodies to species-specific rickettsial antigens. Previously, the Weil-Felix assay, a nonspecific test that detected the presence of cross-reacting antibodies, was used but is no longer recommended due to its low sensitivity and specificity.

Treatment: Doxycycline (2.2 mg/kg every 12 h) for 1–2 weeks is indicated for children of any age along with intensive support of shock and multiorgan failure as necessary. Acute dialysis may be required until renal function returns to normal.

13.10 Enteric Pathogens

Enteric infections can cause hypovolemia and acute kidney injury of prerenal etiology. In addition, *Escherichia coli*, *Yersinia*, *Campylobacter*, and *Salmonella* have been associated with different forms of glomerulonephritis. *Shigella dysenteriae* and *E. coli* 0157:H7 can cause diarrhea-associated HUS (refer to Chap. 3.7.4).

13.10.1 Salmonellosis

Typhoid fever caused by *Salmonella typhi* is characterized by fever, malaise, and hepatosplenomegaly. Renal involvement is rarely severe, but >50 % show asymptomatic glomerular involvement with abnormal urine analysis (hematuria, proteinuria, usually <1 g/24 h) during the febrile phase. Acute tubular necrosis might occur in most severe cases. Significant renal disease occurs in <6 % with mesangial proliferation and IgM, IgG, and C3 deposition on IF. *Salmonella* Vi antigens have been demonstrated within the glomeruli. Recovery is usually complete and occurs in 2–3 weeks.

13.10.2 Yersinia Infections

Infections caused by *Yersinia enterocolitica* and *Y. pseudotuberculosis* are characterized by fever, abdominal pain, and diarrhea. Transient proteinuria is found in

25 % of acute infections and elevated creatinine in 10 % of cases. Renal biopsy shows mild mesangial glomerulonephritis or IgA nephropathy. *Y. pseudotuberculosis* is also known to cause tubulointerstitial nephritis causing acute kidney injury, especially in children. Mild degrees of proteinuria, glycosuria, and sterile pyuria are also found. AKI develops 1–3 weeks after onset of fever and follows a benign course with complete recovery.

13.10.3 Cholera

Epidemic diarrheal illness caused by *Vibrio cholerae* may sometimes be associated with acute kidney injury and rhabdomyolysis. Rapid intervention with fluid replacement is essential to prevent hypovolemic shock and circulatory collapse in most cases. Doxycycline is useful in some cases for shortening the duration of symptoms.

13.11 Renal and Genitourinary Tuberculosis

Renal tuberculosis (TB) is rarely reported in children, and most cases are reported in adults. In recent years, there appears to be a reemergence of renal tuberculosis due to HIV infection. Following hematogenous spread, several renal cortical foci are formed, although these foci have little tendency to progress. Renal involvement usually occurs years to decades after the primary infection, although several cases of short incubation period in children are reported. Among very young children, renal tuberculosis is seen along with military TB.

Clinical Features: The onset may be insidious and may manifest when the bladder is involved. Urinary frequency, dysuria, hematuria, and flank pain may be seen, along with fever, loin pain, and hypertension. Lab evaluation can reveal sterile acid pyuria and hematuria. AKI due to tuberculosis is very rare. Tuberculosis of the epididymis presents as a scrotal swelling with later development of a hard, craggy epididymis. Caseation necrosis leads to the development of sinuses.

Diagnosis: The definitive diagnosis is the isolation of *Mycobacterium tuberculosis* from the urine or directly from the renal or genitourinary lesion. Newer modalities like PCR are useful, although limited by availability factors and false-positive rates. Needle aspiration or renal biopsy may demonstrate granulomas or acid-fast bacteria. Tuberculous skin test (TST) may be used as an adjunct diagnostic aid. Imaging studies such as ultrasound and CT scan may be helpful in identifying kidney lesions. The most common findings of renal parenchymal masses, scarring, calcification, cavitation, and hydronephrosis due to stricture may be seen in imaging studies.

Renal Pathophysiology: In classical TB of the kidney, renal damage is caused by obstruction or massive caseous destruction. Mesangial proliferation, which is not usually seen with other forms of interstitial nephritis, is also common. TB granulomatous interstitial nephritis has been well described and is thought to be secondary to the immune response against TB.

Treatment: Treatment includes combination antituberculosis therapy for 12 months. Either daily or intermittent therapy has been recommended. Reconstructive surgery is useful in the case of ureteral stricture or contracted bladder. Radical surgery in the form of a nephrectomy may be done for a nonfunctioning kidney especially if hypertension is present.

13.12 Viral Hemorrhagic Fevers

Viral hemorrhagic fevers are diseases caused by different families of RNA viruses that are transmitted through the bite of an infected arthropod or by inhalation of particles of rodent excreta.

13.12.1 Dengue

Introduction: Dengue virus is a *flavivirus* transmitted by the mosquito *Aedes aegypti* and other *Aedes* species. There are four dengue serotypes that are closely related antigenically; infection with one serotype produces lifelong immunity to that serotype but poorly protects against the remaining serotypes. The global dengue belt is depicted in Fig. 13.6.

Clinical Features: After an incubation period of 3–14 days, the infection is characterized by biphasic fever, malaise, rash, and lymphadenopathy. The classic features of dengue hemorrhagic fever (DHF) are fever, minor or major hemorrhagic manifestations, thrombocytopenia, and evidence of increased capillary permeability which can result in serositis, hypoalbuminemia, and raised hematocrit. In 20–30 % of cases, DHF is complicated by shock (dengue shock syndrome) as well as hypotension.



Fig. 13.6 The global dengue belt (Source: WHO 2008)

Renal Involvement: Renal involvement is not common. Severe dengue infections can give rise to shock and multiorgan dysfunction, leading to prerenal AKI and acute tubular necrosis. Other renal manifestations include azotemia, proteinuria, glomerulonephritis, and hemolytic-uremic syndrome.

Renal Pathophysiology: Histopathology shows mesangioproliferative glomerulonephritis, endothelial swelling, interstitial edema, perivascular infiltration by mononuclear cells, and tubular degeneration. IF shows deposits of IgM, IgG, and C3.

Diagnosis: Clinical criteria are used in making a diagnosis of dengue fever and may be confirmed by lab parameters. In early infection, viral antigen detection in serum or cerebrospinal fluid using immunofluorescence or ELISA may be helpful. PCR may also be used for virus detection. Serological diagnosis may be performed once the fever has subsided and the second week has begun.

Treatment: Management of dengue is supportive and includes fever control, fluid management, and control of bleeding. Fluid management that is guided by clinical response and serial hematocrit levels is currently practised. Full management guidelines may be found in the WHO 2009 dengue management document. Renal replacement therapy is rarely indicated unless there is fluid overload or severe multiorgan failure.

Prognosis: Complete recovery is the norm with adequate supportive management.

Dengue-Like Viruses: **These** are distributed globally and can have similar clinical manifestations. Some examples are as follows:

- Chikungunya (Togavirus)—Africa, India, and Southeast Asia
- O'nyong-nyong (Togavirus)—East Africa
- West Nile fever (Flavivirus)—Europe, Africa, Middle East, India, and North America

13.12.2 Hantavirus

Introduction: Hantavirus infection is a rare tropical disease of hemorrhagic fever with renal syndrome caused by an RNA virus in the Bunyaviridae family. Previously, hantaviruses have been recognized to cause two separate syndromes: hemorrhagic fever with renal syndrome (HFRS) in Eurasia and hantavirus pulmonary syndrome (HPS) in the Americas, although this dichotomy is increasingly becoming indistinct as the disease has overlapping features and is found in other parts of the world.

Transmission: Rodents are the reservoir; infection to humans occurs via inhalation of rodent excreta or direct inoculation through skin cuts or abrasions.

Clinical Features: After incubation period of 2–5 weeks, the disease presents with flu-like symptoms. In hantavirus pulmonary syndrome, severe respiratory distress may occur. In severe cases, thrombocytopenia and disseminated intravascular coagulation (DIC) occur.

Renal Involvement: Renal involvement is common with proteinuria, hematuria, pyuria, and decreased GFR. In severe cases, increased vascular permeability and vascular endothelial injury result in hypovolemia, decreased renal perfusion, and acute kidney injury.

Renal Pathophysiology: Histopathology shows acute tubular necrosis, interstitial edema and hemorrhages, and later interstitial monocyte infiltration. Glomerular changes are less remarkable, showing mild hypercellularity and IgM, IgG, and C3 deposits.

Diagnosis: Serological tests are used for diagnosis.

Treatment: There is no specific treatment for the virus; dialysis and supportive measures for renal failure may be required.

Prognosis: Recovery is generally complete; chronic renal failure and hypertension are rare.

13.12.3 Yellow Fever

Introduction: Yellow fever is endemic in the African subcontinent and is caused by the yellow fever virus, belonging to family Flaviviridae and transmitted by *Aedes aegypti* mosquito. Despite the presence of the vector, this disease is not seen in Asia.

Clinical Features: The spectrum of clinical manifestations is variable, ranging from mild febrile illness to severe hemorrhagic fever.

Renal Involvement: Acute kidney injury with oliguria may occur within 5 days of the severe form of the disease with hemorrhagic manifestations, jaundice, and DIC.

Renal Pathophysiology: Histology may show features of acute tubular necrosis in severe cases.

Diagnosis: Serology with detection of specific IgM is the main method of diagnosis, although sometimes PCR may also be used.

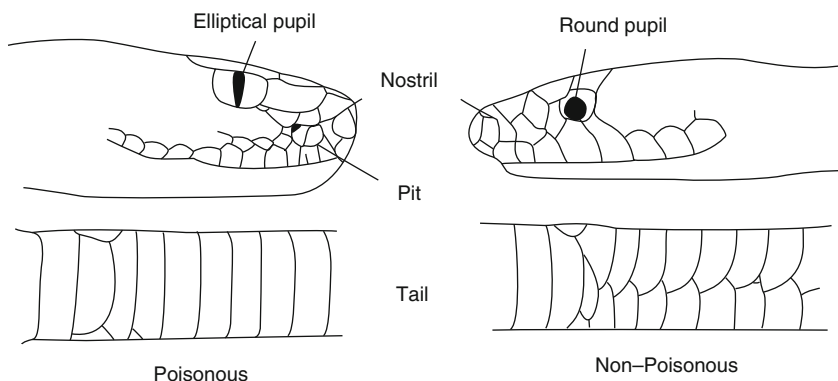
Treatment: Management is mainly supportive and involves treatment of AKI; renal replacement may be necessary in severe cases.

13.13 Snakebite Nephropathy

Introduction: Snakebites are common in the tropics and are caused by either hemotoxic or myotoxic snakes. Most bites are attributed to snakes belonging to Colubridae, Elapidae, Viperidae, and Hydrophidae families. *Bothrops* and *Crotalus* snakes are common in Latin America. For differentiation between poisonous and nonpoisonous snakes, refer to Figs. 13.7.

Clinical Features: Clinical symptoms can vary from local pain and swelling to systemic involvement with hypotension, hemorrhage, disseminated intravascular coagulation, abdominal pain, central nervous system symptoms, and paralysis.

Renal Involvement: Proteinuria, hematuria, pigmenturia, and acute renal failure are common renal manifestations. Proteinuria is usually transient and mild (<500 mg/day), except after Russell's viper bites where nephrotic range proteinuria may be seen. Hematuria (either microscopic or macroscopic) is often seen after hemotoxic snakebites, the incidence as high as 35 %. Pigmenturia (hemoglobinuria or myoglobinuria) is associated in occurrence with intravascular hemolysis or rhabdomyolysis, respectively.



Figs. 13.7 Distinguishing a poisonous from a nonpoisonous snake. (1) Pupil shape: poisonous snakes have elliptical pupils as opposed to round pupils in nonpoisonous snakes. (2) A distinctive nostril or “pit” is seen in poisonous snakes. (3) Scale arrangement: the underside scales are arranged in a single row in poisonous snakes (Source: WHO)

Acute kidney injury (AKI) manifests as oliguria, hyperkalemia, and hyperuricemia, with high CPK and LDH levels, and may be due to several reasons:

1. Shock leading to prerenal AKI.
2. Hemoglobinuria due to hemolysis and myoglobinuria due to rhabdomyolysis.
3. DIC with fibrin thrombi in the glomeruli leading to microangiopathic hemolytic anemia and thrombocytopenia, with a hemolytic-uremic syndrome-like picture.
4. Direct nephrotoxicity of the venom.
5. Sepsis and hypersensitivity to antivenom are rare causes.

Renal Pathophysiology: Snake venoms can cause cellular injury through enzymes and cytokines and initiate a sepsis-like process. AKI can occur due to shock or due to intravascular hemolysis (hemotoxic snake) or rhabdomyolysis (myotoxic snake).

Renal Histopathology: Renal biopsy and histology can show a varied picture:

1. Tubulointerstitial: most common; degeneration of tubular cells, necrosis, interstitial infiltrates, and edema.
2. Glomerular: focal segmental mesangial proliferation, areas of necrosis, thrombosis, and mesangiolysis. IF may show IgM and C3 deposits occasionally.
3. Cortical necrosis: necrosis of all elements with thrombi in the vessels.
4. Vascular: segmental necrotizing vasculitis.

Treatment: Management includes specific antivenom treatment; monovalent antivenoms are preferred over polyvalent. In situations where antivenom is not available, plasmapheresis or blood exchange has been used. Early and frequent peritoneal dialysis or hemodialysis is important for survival. Urine alkalization has a role if there is pigmenturia or if the snake is known to be myotoxic/hemotoxic and renal failure is not yet established. Caution is necessitated as administration of sodium bicarbonate in the setting of acute renal failure can be dangerous, leading to further fluid overload and hyperosmolality.

Prognosis: With adequate treatment, renal recovery is generally complete and takes 2–4 weeks. Residual renal dysfunction and cortical calcification may be sequelae of cortical necrosis.

13.14 Scorpion Bite Nephropathy

Certain scorpions present in tropical countries may be responsible for causing acute kidney injury following a sting. The onset of disease is characterized by the occurrence of hemoglobinuria within 24 h of the sting. Other manifestations include oliguria, edema, hemolytic anemia, and hemolytic jaundice. Renal pathophysiology includes acute tubular necrosis and disseminated intravascular coagulation. AKI can develop within a few days after the sting. Renal biopsies often show mesangial proliferation, variable degrees of tubular changes, and mild interstitial infiltration.

13.15 Natural Medicines Causing Nephropathies

The use of alternative medicines derived from plants and animals is widespread globally, particularly in the tropics. In India and Africa, up to 60–80 % of the population depend on traditional healers and untested herbal medications. These medications are not tested for safety, and since the kidney plays an important role in their metabolism and excretion, acute kidney injury is a common manifestation of their toxicity. In addition, there is easy availability of over-the-counter medications, which may be either allopathic approved medications which are used without a valid prescription or indigenous medications which can cause renal injury. The usual renal lesions include acute tubular necrosis, cortical necrosis, and interstitial nephritis. A high index of suspicion is required to prevent missed diagnosis and to reduce mortality.

Natural medicine	Indications for use	Mechanism of kidney injury
St John's wort, derived from <i>hypericum perforatum</i>	Depression and anxiety	Induces cytochrome P450 activity. Can precipitate AKI in kidney transplant patients due to allograft rejection
Alfalfa juice, noni juice	Nutritional supplement	Hyperkalemia
Saw palmetto/chlorophyll	Benign prostatic hyperplasia	Hyperkalemia
Ginkgo biloba	Memory stimulant	Hemorrhagic complications
Cape aloe (aloin or aloe extract)	Hypertension, eczema, constipation	Hemorrhagic gastroenteritis and acute tubular necrosis
Propolis	Anti-inflammatory, antibiotic, and dietary supplement	Acute kidney injury

Natural medicine	Indications for use	Mechanism of kidney injury
Hydrazine sulfate	Cancer cure	Acute kidney injury
Cat's claw	Cirrhosis, gastritis, gonorrhea, and rheumatism	Acute kidney injury
Aristolochia pistolochia	Weight loss supplement	Acute kidney injury
White willow bark	Back pain, fever, osteoarthritis, headache, and dysmenorrhea	Acute kidney injury
Raw carp bile	Fever, cough, hypertension, stress	Acute kidney injury

Conclusions

Tropical diseases are a well-known cause of acute kidney injury. However, the majority are preventable with early diagnosis and treatment. In almost all cases, treatment of underlying disease and providing supportive care are critical in alleviating the renal damage. Appropriate referral and judicious use of fluids, electrolytes, and renal replacement therapy are major contributory factors towards an uneventful recovery in most cases.

Suggested Reading

- Andrade L, de Francesco DE, Seguro AC (2008) Leptospirosis nephropathy. *Semin Nephrol* 28(4):383–394
- Avner ED (ed) (2009) *Pediatric nephrology*. Springer, Berlin
- Burdmann EA (2008) Acute kidney injury in the tropics. *Semin Nephrol* 28(4):319
- Das BS (2008) Renal failure in malaria. *J Vector Borne Dis* 45(2):83–97
- Gearry DF, Franz S (eds) (2008) *Comprehensive pediatric nephrology*. Elsevier Health Sciences, Philadelphia
- Guerrant RL (ed) (2006) *Tropical infectious diseases*. Elsevier, Inc, Philadelphia
- Jha V, Rathi M (2008) Natural medicines causing acute kidney injury. *Semin Nephrol* 28(4):416–428
- Lima EQ, Nogueira ML (2008) Viral hemorrhagic fever-induced acute kidney injury. *Semin Nephrol* 28(4):409–415
- Nguansangiam S, Day NP, Hien TT, Mai NT, Chaisri U, Riganti M et al (2007) A quantitative ultrastructural study of renal pathology in fatal *Plasmodium falciparum* malaria. *Trop Med Int Health* 12(9):1037–1050
- Sarah L, Larry P, Charles P (eds) (2008) *Principles and practice of pediatric infectious diseases*, 3rd edn. Elsevier, Philadelphia
- Schrier RW (ed) (2007) *Diseases of the kidney and urinary tract*. Lippincott Williams & Wilkins, Philadelphia
- Sitprija V (2006) Snakebite nephropathy. *Nephrology (Carlton)* 11(5):442–448
- World Health Organization (2009) *Dengue guidelines for diagnosis, treatment, prevention and control*. World Health Organization, Geneva, Available at: www.searo.who.int/LinkFiles/Dengue_Guideline-dengue.pdf