CHAPTER 85

# Tropical Infections Causing Acute Kidney Injury

*Nattachai Srisawat, Sadudee Peerapornratana, and Somchai Eiam-Ong*

**OBJECTIVES**

This chapter will:

1. Provide an overview of tropical areas and tropical infections causing acute kidney injury (AKI).
2. Describe epidemiology, clinical features, pathogenesis, and management of common tropical infections causing AKI, including leptospirosis, malaria, dengue, and hantavirus infection.
3. Explain the role of renal support in limited resource areas, including tropical areas.
4. Provide an example of long-term outcomes of AKI patients who recover from tropical infections causing AKI.

The tropics is an area of the Earth around the equator. This area is located between the Tropic of Cancer in the northern hemisphere at 23°26′13.8″ N and the Tropic of Capricorn in the southern hemisphere at 23°26′13.8″ S. These latitudes correspond to the axial tilt of the earth. The tropics includes all the areas on the Earth where the sun reaches a subsolar point, a point directly overhead at least once during the solar year. This zone comprises the northern part of Australia, most of Southeast Asia, South Asia, almost all of Africa, Central American and, South America.

The tropics currently contain nearly 150 countries and account for 40% of the world's population. It is predicted that by 2050 approximately 55% of the world's population will live in the region. Indeed, most of the countries in this region have been grouped by the World Bank into low to low-middle income countries and have limited access to many services, including healthcare.

The World Health Organization (WHO) has used the terminology "neglected tropical diseases," or NTDs, to describe a diverse group of communicable diseases. NTDs mainly affect populations living in poverty, without adequate sanitation and in close contact with infectious vectors and domestic animals and livestock. Neglected zoonotic diseases (NZDs) are a critically important subset of NTDs.

## TROPICAL INFECTIONS ASSOCIATED WITH ACUTE KIDNEY INJURY AND "ONE HEALTH" PERSPECTIVE

The predominant cause of AKI in developing countries is community-acquired acute kidney injury (AKI), one of the major causes of which is tropical infectious diseases. This is in contrast to AKI in developed countries, where hospital-acquired AKI is a predominant cause of AKI.[1]

Therefore prevention by using the "One Health" perspective is the key to success in controlling infection-related AKI in the tropics. The "One Health" perspective comprises the aspects of human, animal (reservoir), and environment factors.[2] The "One Health" working definition states that it is feasible to integrate human, animal, and environmental health efforts to predict and control certain diseases at the human– animal–ecosystem interface; integrated approaches that consider human, animal, and environmental health components can improve prediction and control of certain diseases.

Leptospirosis and malaria, two of the most common tropical infections causing AKI, are an excellent example for the "One Health" approach, in which the relationship between humans, animals, and ecosystems is studied to improve knowledge on a disease and to enhance collaborative intersectoral and multidisciplinary control strategies.

Socioeconomic drivers include living in dense urban or peri-urban areas with inadequate waste collection and sanitation. Many of the tropical infections causing AKI have been linked to poverty, lack of water and sanitation, and poor housing conditions.[3] Heavy rains or floods have been linked to a higher number of cases of leptospirosis. Alkaline and neutral soil are suspected of promoting a longer survival of this bacteria.[2,4] Leptospirosis also is considered as an occupational disease, affecting rice laborers, sewer workers, animal handlers, and gold miners. A better understanding of the drivers for leptospirosis would provide crucial information for decision makers to be able to target risk areas for priority interventions.

In malaria, the main transmission route is mosquito bite. Data from systematic review showed that climate change, lack of preventive tools such as bed nets, repellants, poor infrastructure, less qualified healthcare professionals,

noncompliance, and lack of efficacy of drugs play an important role in malarial transmission.[3,5]

Indeed, to compete with these types of zoonosis diseases, the current gaps in scientific and technologic knowledge that may delay the detection of cases and limit surveillance programs must be addressed. Finally, vaccines have been identified as the perfect key instrument to overcome all tropical infections causing AKI but are not available at this time.

## Overview of Tropical Infections Causing Acute Kidney Injury

Tropical infection is one of the common causes of AKI and is recognized as community-acquired renal emergency in tropical countries.[6,7] Not only infection-related but also non–infection-related causes such as snake bite toxins, plant toxins, and chemical toxins are common causes of AKI in tropical areas. There are only a few reports that have studied the impact of tropical infection causing AKI on a multinational level. A recent major report from 0by25 Global Snapshot team revealed that from a total of 4105 AKI cases, 50% came from tropical areas (13% from Africa, 14% from Latin American/Caribbean, 4% from Oceania/southeast Asia, and 19% from south Asia). As previously mentioned, most of the tropical countries in this study were defined as low-income countries and lower middle-income countries (LLMIC). Although dehydration was the leading cause of AKI (nearly 50%), sepsis, pregnancy-related AKI, and envenomation were more common in LLMIC than other income areas.[8]

The causes of tropical infections causing AKI in tropical countries can be divided broadly into those caused by viruses, bacteria, and parasites (Box 85.1). The leading causes are leptospirosis, malaria, dengue virus, and hantavirus. Distribution of these infections also varied by geographic area. Leptospirosis-associated AKI is highly prevalent in the Caribbean, South America, south Asia, and southeast Asia. Malaria-associated AKI is highly prevalent in sub-Saharan Africa, southeast Asia, the Caribbean, and South America. Dengue-associated AKI is highly prevalent in the Caribbean, South America, and southeast Asia. Hantavirus-associated AKI is highly prevalent in East Asia (Fig. 85.1).

**BOX 85.1**

**Specific Infections in Tropical Infections Causing Acute Kidney Infection**

**Viral Infections**
- Dengue virus[a]
- Hantaan virus

**Bacterial Infections**
- Leptospirosis[a]
- *Burkholderia pseudomallei*
- *Orientia tsutsugamushi* (scrub typhus)
- *Salmonella*
- *Shigella*

**Parasitic Infections**
- *Plasmodium falciparum*[a], *Plasmodium vivax, Plasmodium knowlesi*
- *Wuchreria bancrofti*
- *Brugia malayi, Brugia timori*
- *Leishmania donovani* (kala-azar)

[a]Common cause.

## Clinical Features, Pathogenesis, and Management of Common Tropical Infections Causing Acute Kidney Injury

### *Leptospirosis and Acute Kidney Injury*

**EPIDEMIOLOGY.** Leptospirosis is an important zoonosis, especially in tropical areas. However, with the impact of world globalization, there are also reports of this disease as sporadic cases in developed countries. A recent report has shown that the endemic area of leptospirosis includes the Caribbean and Central and South America, as well as southeast Asia and Oceania.[9] Kidney injury with hyperbilirubinemia represents a severe form called Weil syndrome.

AKI is one of the most serious complications of leptospirosis. The incidence of AKI in leptospirosis by using the standard AKI criteria was up to 84%.[10] This is approximately two times higher than the AKI incidence in the intensive care unit (ICU).[11] This specific setting injures the kidney by direct effect, direct invasion, and indirect effect, such as dehydration, rhabdomyolysis, and bleeding.[12]

**CLINICAL FEATURES.** Renal manifestations of leptospirosis-associated AKI can vary from mild AKI to severe AKI, requiring renal replacement therapy (RRT). Not only kidney injury but also tubular dysfunction, mainly at the proximal tubule, are the common features of leptospirosis-associated AKI.

Hypokalemia is one of the most unique features of renal tubular dysfunction in leptospirosis and is found in nearly 50% of cases. Leptospirosis-associated AKI is usually nonoliguric. This finding is independent from its severity, hypercatabolism, rhabdomyolysis, and acidosis.[13] Kositseth et al. reported that 75% of leptospirosis patients had hypermagnesuria, whereas 50% of patients had decreased the threshold of tubular reabsorption of phosphate.[14] These abnormal findings were improved significantly within 2 weeks after admission. Alterations such as bicarbonaturia, glycosuria, and reductions in proximal reabsorption of sodium, uric acid, and phosphate excretion have been observed. Moreover, a defect in the urinary concentration can persist for a prolonged period.

Mild active urinary sediments (pyuria, hematuria, bile pigment, and granular cast) and mild proteinuria (less than 1 g/day) usually are observed in the urinalysis.

AKI usually develops at the early phase of infection. A recent report by Srisawat et al. indicated that most of the patients had AKI on the first day of admission.[15]

**PATHOGENESIS**

***Direct kidney damage: acute interstitial nephritis.*** Leptospira in the renal tissue triggers a process of acute interstitial nephritis, the key mechanism of AKI in leptospirosis.[16] A study in the past showed the evidence of higher leptospiral load in kidney than other organs.[16a]

Study of *Leptospira* in kidney rats has shown that *Leptospira* penetrate capillary lumen on the second day and then enter in the renal interstitial tissue, causing interstitial edema at the end of first week. After that, *Leptospira* adhere to the renal tubular epithelial surface and cross to the tubular lumen in the second week. The outer membrane of *Leptospira* contains antigenic components, including lipoproteins, lipopolysaccharides and peptidoglycans, and endotoxins that

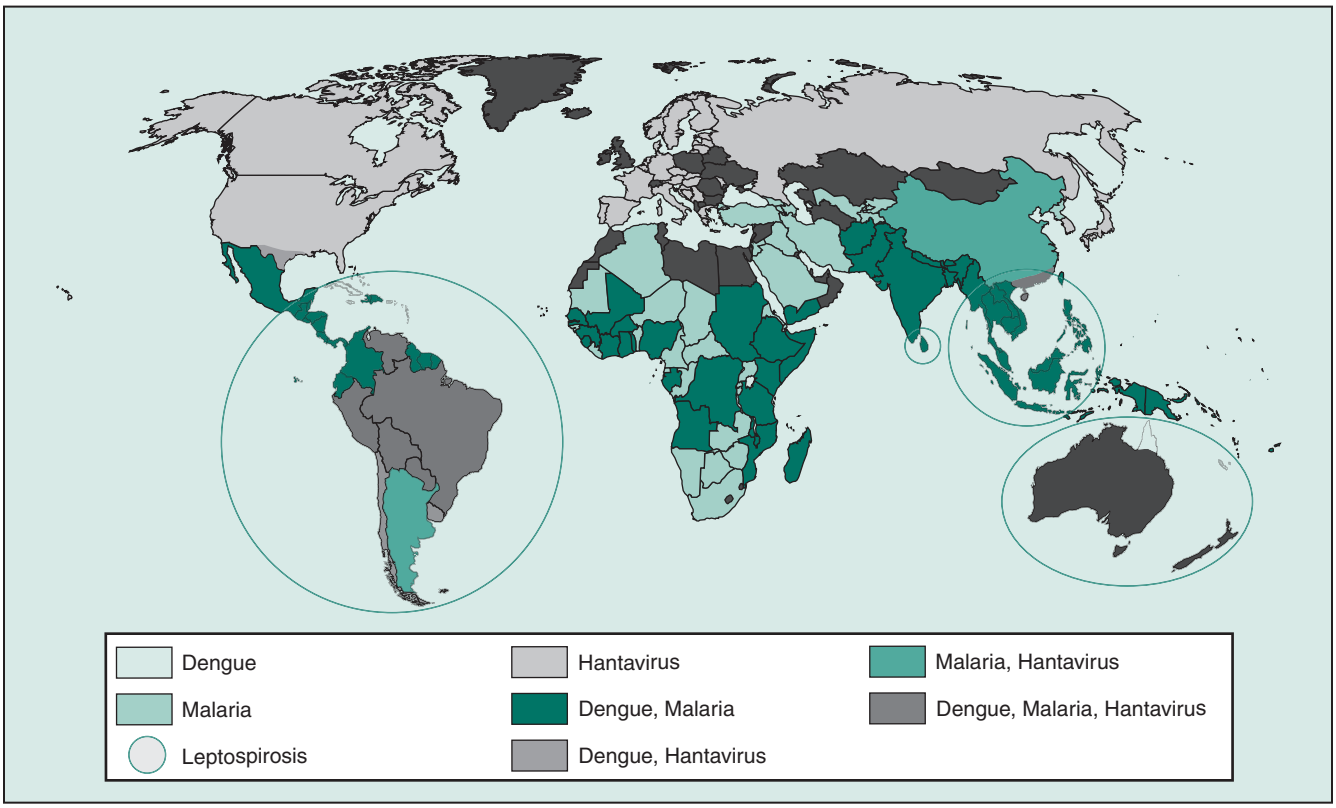


**FIGURE 85.1** Prevalence estimates of major tropical infection causing acute kidney injury (AKI). Leptospirosis-associated AKI is highly prevalent in the Caribbean, South America, South Asia, and southeast Asia. Malaria-associated AKI is highly prevalent in sub-Saharan Africa, southeast Asia and Caribbean, and South America. Dengue-associated AKI is highly prevalent in the Caribbean, South America, and Southeast Asia. Hantavirus-associated AKI is highly prevalent in East Asia.

can account for kidney injury, leading to tubular dysfunction and inflammation. Several outer membrane proteins (OMPs), such as lipL32, Loa22, LipL41, Lig family, LipL36, LipL21, and LipL46 of pathogenic species, have been identified at the proximal tubule and interstitium of infected animals.[17] Among them, LipL32 is one of the most important OMPs. The LipL32 will bind to Toll-like receptor 2 (TLR2), not TLR4, leading to activation nuclear factor kβ (NF-kβ). This will stimulate the production of proinflammatory cytokines and chemokines, such as tumor necrosis factor-alpha (TNF-α), inducible nitric oxide, monocyte chemotactic protein-1, T cells (RANTES), and CXCL2/MIP-2 for recruiting inflammatory cells.[18] TNF-α is the most investigated cytokine in leptospirosis. It is an inflammatory cytokine produced after TLR4 stimulation[19] (Fig. 85.2).

***Indirect kidney damage: hemodynamic instability.*** The pattern of hemodynamic instability in leptospirosis depends on the severity of disease and complications. Siriwanij et al. reported three patterns of hemodynamic changes during severe leptospirosis.[20] The first, which was the most common pattern, was decreased systemic vascular resistance (SVR) and mean arterial pressure, increased cardiac index (CI), but normal pulmonary vascular resistance (PVR) and pulmonary capillary wedge pressure (PCWP). The second pattern, which was found in patients with pulmonary complications, was normal SVR and CI, with increased PVR. The last pattern in the setting of hyperbilirubinemia was normal or slightly increased SVR. There were decreases in CI and mean arterial pressure (MAP), although there were no changes in PVR and PCWP.[20]

***Hyperbilirubinemia.*** Hyperbilirubinemia is common in severe leptospirosis. Sitprija et al. demonstrated the toxicity of hyperbilirubinemia in the model of obstructive jaundice from cholangiocarcinoma. Bilirubin levels higher than 26 mg/dL impaired glomerular filtration rate (GFR) and ability to concentrate urine.[21]

***Rhabdomyolysis.*** Rhabdomyolysis is another common indirect cause of kidney injury. The incidence of rhabdomyolysis in leptospirosis is up to 60%. Rhabdomyolysis causes kidney injury via renal vasoconstriction, tubular obstruction, and direct toxicity.[22–24]

Fig. 85.2 demonstrates the pathogenesis of leptospirosis-associated AKI.

**MANAGEMENT.** The early diagnosis and institution of appropriate therapy are the most important points in managing leptospirosis and leptospirosis-associated AKI. Srisawat et al. recently reported the role of urine and plasma neutrophil gelatinase-associated lipocalin (uNGAL and pNGAL, respectively) in the early diagnosis of leptospirosis-associated AKI. The AUC-ROC values of uNGAL and pNGAL for diagnosis of AKI were 0.91 and 0.92, respectively.[15]

Consensus about the use of antibiotics for treating leptospirosis is still lacking. A recent meta-analysis has not found sufficient evidence to indicate the use of antibiotics in leptospirosis; however, it was concluded that antibiotic therapy in leptospirosis seemed to have more benefits than drawbacks.[25] Antibiotic therapy was associated with a significant reduction in leptospira antigen. Based on the recommendation of the World Health Organization of 2003, severe leptospirosis should be treated with intravenous

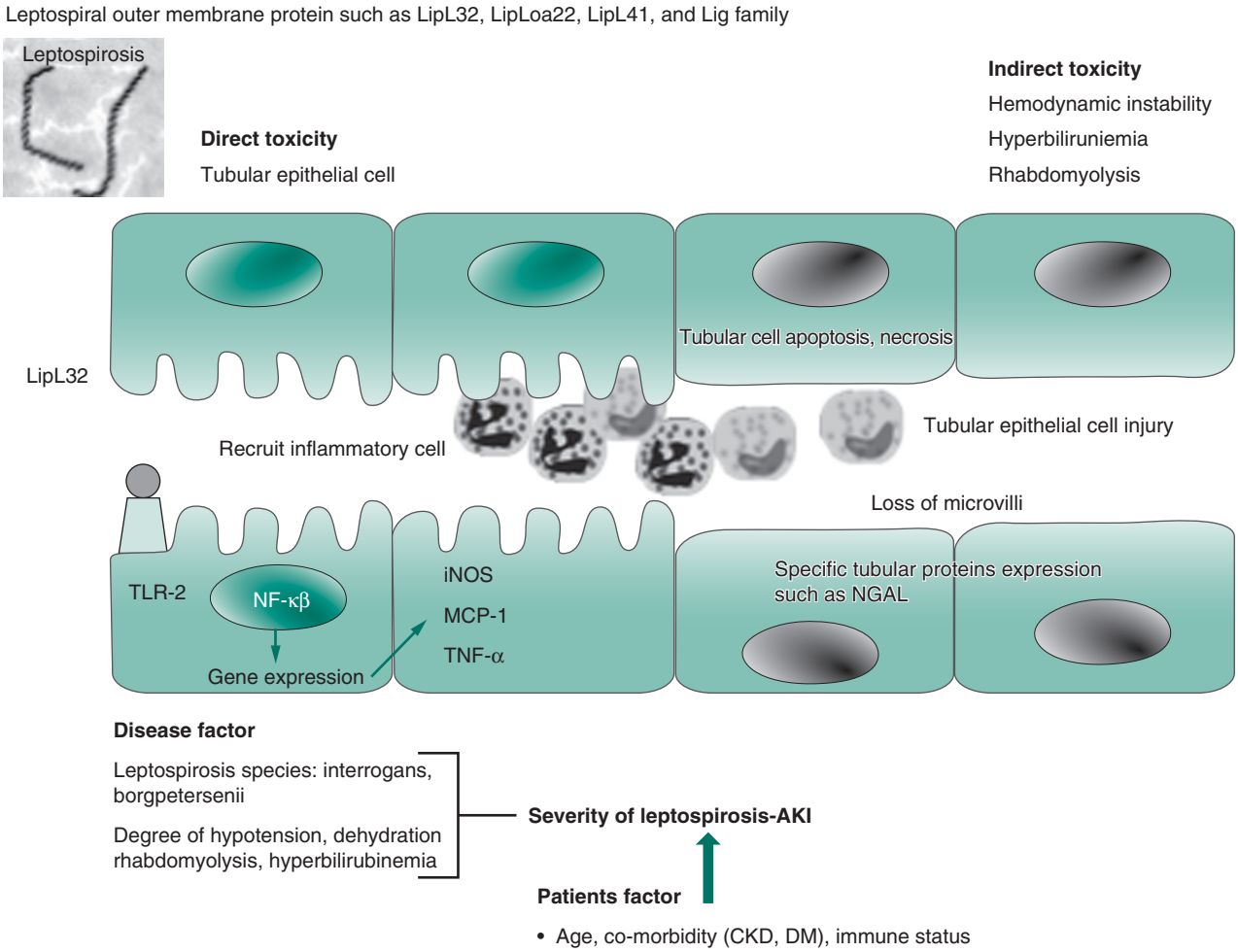


**FIGURE 85.2** Pathogenesis of leptospirosis-associated acute kidney injury.

penicillin,[26] ceftriaxone,[27] or cefotaxime,[28] all equally effective. The duration of antibiotic therapy should be 7 days. Oral antibiotics, such as doxycycline, amoxicillin, erythromycin, or azithromycin, are effective in mild cases.[29,30] For prophylaxis of leptospirosis, doxycycline is the mainstay antibiotic.

Recently, Niwattayakul et al. have studied the role of corticosteroid and desmopressin in 68 severe leptospirosis patients with pulmonary involvement. Unfortunately, they could not demonstrate the survival benefit of these two treatments compared with the control group.[31]

## Malaria and Acute Kidney Injury

Tropical and subtropical regions are endemic areas of malaria transmission. Malaria is caused by five species of the genus *Plasmodium*, namely *Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae, Plasmodium ovale,* and *Plasmodium knowlesi*.

**EPIDEMIOLOGY.** There is a trend of reductions in the number of malaria cases as well as deaths over the past 15 years. It was estimated that the number of malaria cases had decreased from 262 million in 2000 to 214 million in 2015 (about 20% reduction), while the number of deaths had decreased from 839,000 to 438,000 (about 50% in death cases). Most cases in 2015 were estimated to occur in the WHO African region (88%) followed by the WHO southeast Asia region (10%) and the WHO eastern Mediterranean region (2%). Similarly, it was estimated that in 2015 most deaths (90%) were in the WHO African region, followed by the WHO southeast Asia region (7%) and the WHO eastern Mediterranean region (2%).

The incidence of malaria-associated AKI widely ranges from 0.5% to 30% in different series, because this depends on the cohort of patients and the criteria used for the definition of AKI.[32]

**CLINICAL FEATURES.** Malaria-associated AKI is caused mainly by *P. falciparum*. However, recent reports have shown that *P. vivax, P. ovale,* and *P. knowlesi* can cause some degree of kidney injury.[33–37] Serum creatinine of more than 3 mg/dL has been used as one definition criteria of severe malaria by WHO.[32,38] It is more common in adults than children and more often in males than females.[39,40]

Although the usual presentation is acute tubular necrosis, a small but significant proportion show glomerular involvement, either acute nephritic syndrome or nephrotic syndrome. Most of AKI complications in malaria results from multiple organ failure and contain poor prognosis. One of the main clinical features in malaria-associated AKI is oliguria and found in about 70%.[40] The mean duration of oliguria ranges from 7 to 10 days.

Not only a cause of AKI, malaria also can induce electrolyte disorders. In contrast to leptospirosis-associated AKI, malaria-associated AKI causes hyperkalemia more commonly than hypokalemia. This is associated with the clinical feature of oliguria. Hyponatremia occurs in 25% to 60%[41,42] and is caused by hemodilution and sodium wasting, not the increase of vasopressin hormone as the main mechanism.[41] Furthermore, hypoxia from the combination of volume depletion, hypotension, pulmonary edema, clogging of the capillaries by cytoadhered red blood cells and mononuclear cells results in severe hyperlactatemia, which was related to poor prognosis.[43] Risk factors to develop AKI in malaria patients are pregnancy, jaundice, prolonged hypotension, and nonsteroidal antiinflammatory (NSAID) exposure.

**PATHOGENESIS.** The pathogenesis of malaria-associated AKI is multifactorial, mainly from indirect effects, including hemodynamic alteration, cytoadherence effect of parasitized red blood cells (PRBCs) to the vascular endothelial cells, hypercytokinemia, intravascular hemolysis, and rhabdomyolysis.

The pattern of hemodynamic changes is dependent on the severity of disease and its associated complications.[20] When malarial infection is mild (<1% of infected erythrocytes), renal blood flow (RBF) and GFR are normal, and blood volume is either normal or slightly increased. When malarial infection is moderately severe (1% to 5% of infected erythrocytes), RBF and GFR decrease, and blood volume increase. In patients with severe malarial infection (>5% of infected erythrocytes), blood volume drops, and RBF and GFR are greatly diminished.[44] These changes result from hemorrheologic alteration and cytoadherence of red blood cells, leading to kidney injury.

The part of malaria called *variant surface antigens,* expressed on the PRBC surface, mediate the adhesion of PRBCs to the host vascular endothelial receptors in various organs such as the brain, liver, lung, spleen, intestine, and kidney. When compared with the brain, sequestration of PRBCs in glomerular and tubulointerstitial capillaries has been shown in a lesser degree.[45–48]

There are a few reports regarding the role of cytokines in the pathogenesis of malaria-associated AKI. The levels of inflammatory cytokines, such as TNF-α, IFN-γ, IL-1α, IL-6, and IL-8 are increased in malaria. Moreover, higher blood concentrations of these proinflammatory cytokines have been observed in severe complications of malaria.[49–52]

**MANAGEMENT.** The management of malaria-associated AKI requires careful and meticulous management of several problems. Early and prompt decisions and institutions are the hallmark of a better prognosis. The outlines of treatment guidelines include the following: (1) institution of appropriate antimalarial, (2) maintenance of fluid and electrolyte levels, (3) renal replacement therapy as indicated, (4) treatment of associated complications, and (5) management of infection including pneumonia. Drugs to be avoided in malaria patients because they may impair renal function are as follows: nephrotoxic drugs such as aminoglycosides should be avoided if AKI is suspected or anticipated, NSAID drugs should not be given because they may precipitate prerenal azotemia to ischemic AKI, and angiotensin-converting enzyme inhibitors and cyclooxygenase inhibitors.

## Dengue Infection and Acute Kidney Injury

Dengue infection is one of the most significant human viral mosquito-borne infections. The main pathogen is dengue virus, an RNA flavivirus that comprises four serotypes, DEN-1 through DEN-4. Female *Aedes aegypti* is the main vector. Once infection occurs with one serotype, there will be only lifelong protection to that serotype and a few months for the remaining serotypes.[53,54] Dengue has an incubation period of 3 to 14 days and will replicate in reticuloendothelial system during this phase. The clinical spectrum range from asymptomatic (as many as 50% of individual infections), dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), the most severe form of dengue infection.

**EPIDEMIOLOGY.** Dengue infection is endemic mainly in the tropics and subtropics, with approximately one third of the world population is at risk for dengue infection. The worldwide infection rate approaches 50 to 100 million each year.[55]

The prevalence of AKI in previous studies varied widely because of heterogeneous definitions of AKI, population age group, and the severity of dengue virus infection. Current available data were derived mainly from case reports and retrospective studies. Two studies use the elevation of serum creatinine to more than 2 mg/dL for the definition of AKI and may underestimate the prevalence of AKI.[56,57] However, later studies have applied the Acute Kidney Injury Network (AKIN) criteria and the risk, injury, failure, loss of kidney function, and end-stage acute kidney disease (RIFLE) criteria, which allowed for more diagnosis of AKI.[58,59] In summary, the prevalence of acute kidney injury ranges from 0.2% to 35.7%.

**CLINICAL FEATURES.** Acute tubular necrosis is the major finding of severe dengue infection. This typical finding is a part of multi-organ dysfunction.

Proteinuria is another common finding in DHF, which can be up to 75%.[60,61] Some reports showed this can reach to nephrotic range proteinuria.[62]

Glomerulonephritis such as anti-GBM disease, IgA nephropathy, and lupus nephritis has been reported in dengue infection.[63–65] More common manifestations are hematuria, up to 13%, and decrease of C3 level in 82% of dengue patients.[66] There are only a few studies of renal histology in dengue infection. Boonpucknavig et al. examined kidney tissue from 20 children with DHF and showed the deposition of IgG, IgM, and C3 at the mesangial area in 50% of cases.[67] Electron microscope images from those who had immune complex depositions revealed focal thickening of the glomerular basement membrane, with hypertrophy of mesangial cells at the sites where the immune complex was shown.[67]

Electrolyte disturbances are common in dengue infection, yet frequently unreported. Higher electrolyte imbalances were associated with dengue severity. The most common electrolyte disturbances are hyponatremia and hypokalemia. Hyponatremia may be from plasma leakage, hypotonic fluid therapy, or renal salt wasting.

**PATHOGENESIS.** The mechanism of kidney injury in dengue infection is poorly understood. Overall, there are two main mechanisms, including direct and indirect effects. Profound hypotension, rhabdomyolysis, and intravascular hemolysis are well-known indirect effects in tropical infections causing AKI, including dengue infection. However, there was some evidence of dengue virus in the kidney tissue. Boonpucknavig et al. found dense and spheric particles in electron microscopy of 12 DHF patients.[67] The authors hypothesized that these particles may be a part of dengue virus. Jessie studied tissue specimens from dengue patients by immunohistochemistry (IHC) and in situ hybridization (ISH) to localize viral antigen and RNA,

respectively.[68] IHC was performed in the specimens obtained from 5 autopsies and 24 biopsies and on 20 blood-clot samples. Viral antigens were demonstrated in various cells including renal tubular epithelial cells.

**MANAGEMENT.** Management of dengue infection is symptomatic, because there is no specific drug to treat dengue virus. Maintenance of hydration is the major concern in the treatment of these patients. Acetaminophen and aspirin should be avoided because of the risk of acute liver failure.

### *Hantavirus and Acute Kidney Injury*

Hantaviruses are enveloped RNA viruses belonging to the family Bunyaviridae. Their reservoir hosts are primarily rodents, shrews, moles, and bats. Despite not causing diseases in rodents, Hantavirus can be transmitted via aerosols of rodent excreta to humans. Human-to-human transmission has not been reported.

The two major clinical syndromes are hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS).

**EPIDEMIOLOGY.** HFRS has been a major epidemic mainly in Asia and Europe. About 100,000 cases of HFRS are documented annually worldwide,[69] most of which occur in China, Korea, Russia, Finland, and Sweden. HFRS is caused primarily by Hantaan virus (HTNV) and related viruses in Asia, and by Puumala virus (PUUV) and Dobrava virus (DOBV) in Europe. PUUV is endemic in northern Europe (mostly in Sweden and Finland) and may cause a generally mild form of HFRS, which is also called "Nephropathia epidemica." Seoul virus (SEOV) is globally widespread and may cause moderate HFRS. HTNV or DOBV cause the most severe form of HFRS and have the highest morbidity rates ranging from 5% to 10%.[70]

HCPS is caused by Sin Nombre virus (SNV) and related viruses in North America, and by Andes virus (ANDV) and related viruses in Latin America.

**CLINICAL FEATURES.** The incubation period is approximately 2 to 4 weeks. The clinical course of HFRS is characterized primarily by nonspecific flu-like symptoms (fever, headache, and back pain are common symptoms),[71] circulatory collapse, and hemorrhage. The disease typically progresses through five phases: febrile, shock, oliguria, polyuria, and convalescent, and frequently overlaps in severe cases. Laboratory findings during the acute stage of the disease are anemia, leukocytosis, thrombocytopenia, elevated liver enzymes and serum creatinine, and proteinuria as well as hematuria. Renal involvement in HFRS causes a transient decrease in GFR, proteinuria, microscopic hematuria, and oliguria.[72–74] The renal syndrome begins around the third day of illness. The peak serum creatinine level is reached around the end of the first week.[75] Within 2 to 3 weeks, polyuria and spontaneous recovery of renal function is the typical clinical course of HFRS. The mild form of HFRS *(Nephropathia epidemica)* commonly causes AKI in healthy persons living in endemic regions.

**PATHOGENESIS.** Vasculopathy is thought to be the fundamental pathophysiology of hantavirus infection. The viral particles enter the endothelial cells leading to dramatic vascular endothelial dysfunction, and finally, causing increases in capillary permeability (vascular leakage syndrome) and thrombocytopenia. It also has been suggested that cytotoxic CD8+ T cells and their cytokines trigger capillary leakage. The terminal soluble complement complex also can increase vascular permeability, and complement activation is linked to severity of hantavirus infection.[76] The majority of renal pathology is acute tubulointerstitial nephritis with microvascular inflammation (peritubular capillaritis) without specific glomerular changes.[77,78] The cell infiltration consists of lymphocytes, monocytes, macrophages, and polymorphonuclear cells.[79]

**MANAGEMENT.** Several antiviral drugs have been used in treatment of HFRS and HCPS. Ribavirin has been used in clinical trials and shows that, if starting early during clinical course, it can be effective against hantaviruses causing HFRS.[80] Favipiravir has been reported to have high activity against a panel of Bunyaviruses.[81,82] Interferon-alpha, steroids, and cyclophosphamide have been used in clinical practice for various effects.[69] Monoclonal antibodies against HTNV have been developed and have anti-HTNV activity in vitro and in vivo.

Supportive treatment is still the cornerstone of treatment with a greater reduction of mortality rate. Stabilizing the hemodynamics and oxygenation by invasive and noninvasive monitoring is crucial for maintaining renal perfusion. Fluid resuscitation and electrolyte balance are also important in cases with severe leakage syndrome. Platelet transfusions can be used in severe cases with thrombocytopenia and obvious bleedings. Up to 6% of hospitalized patients with HFRS need RRT.[83] Continuous renal replacement therapy (CRRT) has been used in patients with AKI accompanied with multiorgan dysfunction or fluid overload.

Table 85.1 compares the clinical features of common tropical infections causing AKI.

## ROLE OF RENAL REPLACEMENT THERAPY IN TROPICAL INFECTIONS CAUSING ACUTE KIDNEY INJURY

Currently, renal replacement therapy (RRT) is one of the most important tools to treat AKI including tropical infections causing AKI. In developed countries that have no limited resources, hemodialysis and CRRT are the two major modalities. However, in developing countries, including most tropical countries with limited resources of medical equipment, including RRT treatment. Peritoneal dialysis (PD) is still one of the key RRT modalities in the tropical countries. Possible explanations why PD is still widely used in this region are due to low cost, ease of installing the catheter, and requirement for less sophisticated machines.

### Resources

Information regarding available resources in RRT is extremely crucial. However, there are a few studies to explore the RRT resources in tropical countries. A recent survey study from Latin America countries by Lombardi et al. showed that all units of participants had intermittent hemodialysis (IHD), 41% performed slow extended dialysis (SLED), 30% used PD, and 23% performed CRRT to treat AKI patients who required RRT support.[84] Most RRT patients were treated by nephrologists. Leptospirosis is the leading cause of AKI in this survey. This is in contrast to the data from Western countries. Jones et al. performed a survey study of AKI practice in the UK ICU and found that CRRT was markedly preferred (93%), followed by IHD (4.5%), and less than 1% for SLED.[85] Intensivists took the main response in CRRT

**TABLE 85.1**

**Comparison Clinical Features of Common Tropical Infections Causing Acute Kidney Injury**

| DISEASE | LEPTOSPIROSIS | MALARIA | DENGUE VIRUS | HANTAVIRUS |
|---|---|---|---|---|
| Incidence of AKI | Up to 80% | Up to 30% | Up to 5% | Up to 80% |
| Endemic area | Caribbean islands, Latin America, south Asia, southeast Asia | Sub-Saharan Africa, southeast Asia | Latin America, Caribbean islands, south Asia, southeast Asia | East Asia (China, Korea), Sweden, Finland |
| Genus species cause AKI | *L. interrogans, L. borgpetersenii* | *P. falciparum, P. vivax,* and *P. knowlesi* | Dengue type 1–4 | Hantaan virus, Puumala virus, and Dobrava virus |
| Reservoirs/vectors | Rodents, cattle | *Anopheles* | *Aedes aegypti* | Rodents, shrews, moles, and bats |
| Pathogenesis of AKI | Interstitial nephritis, hemodynamic alteration | Hemodynamic alteration, cytoadherence of RBCs, hypercytokinemia | Hemodynamic alteration, Hypercytokinemia | Endothelial dysfunction |
| Renal features | ATN, tubular dysfunction (hypokalemia) | ATN, tubular dysfunction (hyponatremia, hypo/hyperkalemia) | ATN, proteinuria, glomerulonephritis, hemolytic uremic syndrome | ATIN |
| Treatment | Penicillin G, ceftriaxone | Artesunate, quinine | Supportive care | Supportive care |

*AKI,* Acute kidney injury; *ATIN,* acute tubulointerstitial nephritis; *ATN,* acute tubular necrosis.

management, whereas nephrologists performed IHD. In data from the United States, based on the Acute Renal Failure Trial Network (ATN) study, nearly 100% used IHD, followed by 86.2% using CRRT, and only 24.6% using SLED.[86] Table 85.2 compares the RRT resources among the tropical countries, the United Kingdom, and the United States. With limited resources, early detection and referral of AKI patients are key for success.

The cost of RRT, shortage of dialysis facilities and certified nephrologists, and transportation limitations are substantial obstacles that restrict access to adequate RRT support in tropical regions. In Cambodia, Myanmar, and Vietnam, there were only 10, 28, and 130 dialysis facilities as of 2011, respectively.[87,88] Moreover, hemodialysis facilities are concentrated in urban centers and are often unable to cope with the heavy demand for their services. India has only 900 qualified nephrologists for a country of 1.2 billion people, whereas Pakistan has 250 for about 150 million. More than 90% of nephrologists work in the private sector.[89]

**TABLE 85.2**

**Comparison of Resources Characteristics of Renal Replacement Therapy Between Tropical Countries and Nontropical Countries**

| | TROPICAL COUNTRIES | NONTROPICAL COUNTRIES |
|---|---|---|
| TYPE OF AKI | COMMUNITY ACQUIRED | HOSPITAL ACQUIRED |
| Age group | Young | Elderly |
| Comorbidity | No | Yes |
| Socioeconomic status | Low to middle income | High income |
| Physician in charge | Nephrologist | Intensivist for CRRT, nephrologist for IHD |
| Main RRT modality | IHD, PD | IHD, CRRT (in ICU) |

*CRRT,* Continuous renal replacement therapy; *ICU,* intensive care unit; *IHD,* intermittent hemodialysis; *PD,* peritoneal dialysis.

## Modalities of Choice

There are a few studies to test the efficacy of RRT modality in the setting of tropical infections causing AKI. With limited resources of countries in this region, PD is often the only form of dialysis available.[90]

Phu et al. have raised concerns about the efficacy of PD in septic AKI patients. Patients who received PD had significantly higher mortality than CRRT (CVVH), 47% vs. 15%, $p = .005$; 68% of cases in the study were severe falciparum malaria.[91] The PD technique in this study was less than ideal, with the use of rigid catheters, manual exchanges, and open drainage. Indeed, cloudy dialysate was observed in 40%, potentially representing peritonitis episodes, which may have contributed to poor outcomes in the peritoneal dialysis group.[91] However, a recent meta-analysis by Chionh et al. in 11 studies (7 cohort studies and 4 randomized trials) compared patients who received peritoneal dialysis (n = 392, pooled mortality = 58.0%) or extracorporeal blood purification (n = 567, pooled mortality = 56.1%). There was no difference in mortality between PD and extracorporeal blood purification (odds ratio, 0.96; 95% CI, 0.53 to 1.71).[92] Finally, the International Society of Peritoneal Dialysis has endorsed acute peritoneal dialysis as one standard treatment in AKI setting.[93]

# LONG-TERM RENAL OUTCOME AFTER TROPICAL INFECTIONS CAUSING ACUTE KIDNEY INJURY

Regarding to Kidney Disease: Improving Global Outcomes (KDIGO) AKI guideline 2012 recommendations, AKI patients who recover from kidney injury should undergo follow-up in the next 3 months. This recommendation is based on an observational study.[94] In a cohort of children with AKI discharged from a public-sector hospital in India, proteinuria, hypertension, hematuria, or reduced

**TABLE 85.3**

**Summary of Follow-Up Studies of Leptospirosis-Associated Acute Kidney Injury**

| AUTHOR, YEAR | N | CONTROL | AKI CRITERIA | F/U TIMING | LABORATORY PARAMETERS | FINDINGS |
|---|---|---|---|---|---|---|
| Ghesmian R, 2016[98] | 51 | No | Cr > 1.5 | 1 year | Cr | 16 had renal dysfunction at discharge, 4 at 3 months, and 2 patients at 1 year |
| Herath NJ, 2014[97] | 44 | No | RIFLE criteria | 1 year | Cr, GFR | 9% had persistent renal dysfunction after 1 year |
| Daher EF, 2004[24] | 35 | Healthy 18 cases | Cr > 1.5 | D/C, 3 month, 6 month | SCr, FeNa, FeK, Proteinuria, U/POsm, U pH | U/Posm different between patients and control group at 6 months |

*Cr,* Creatinine; *D/C,* discharge; *FeK,* fractional excretion potassium; *FeNa,* fractional excretion sodium; *F/U,* Follow-up; *GFR,* glomerular filtration rate; *RIFLE,* risk, injury, failure, loss, and end-stage renal disease; *U pH,* urine pH; *U/Posm,* urine-to-plasma osmolarity ratio; *U/POsm,* urine to plasma osmolarity.

GFR were present in 32% of patients after 6 months and in 38% of patients after 10 years.[95] The risk of the future development of CKD is exacerbated by the late presentation of AKI.[96]

There are a few studies on renal function recovery for tropical infections causing AKI. Daher et al. studied 35 patients with leptospirosis-associated AKI. The authors tested creatinine clearance, fractional excretion of sodium and potassium, proteinuria, sodium proximal reabsorption, urinary pH, and the ratio of urinary to plasma osmolality (U/Posm) up to 6 months after discharge. Most of tubular function returns to normal except only urinary concentration.[24] Herath et al. studied[44] leptospirosis-associated AKI patients by follow-up at least for 1 year. Only 9% of patients had abnormal renal functions compatible with early stage CKD, but no one needed long-term dialysis.[97] Ghasemian conducted a longitudinal prospective study in serologically confirmed leptospirosis-associated AKI. Patients with renal failure were followed for 1 year. There were only 2 of 51 cases with persistent serum creatinine higher than 1.5 mg/dL[98] (Table 85.3). The same pattern occurs in malaria-associated AKI, in which AKI will resolve in days to weeks and almost always is completely cured and does not progress to chronic kidney disease.[99]

## Key Points

1. The tropical region contains nearly 150 countries and accounts for 40% of the world's population, and it is predicted that by 2050 approximately 55% of the world's population will live in the region.
2. Tropical infections cause AKI by various types of organisms such as bacteria (leptospirosis, melioidosis), viruses (dengue virus, Hantaan virus), and parasitic infections (*Plasmodium* spp.).
3. The main mechanism of tropical infections causing AKI can be divided into direct effect, such as in leptospira invasion, and indirect effect, such as dehydration, rhabdomyolysis, and intravascular hemolysis.
4. Because of limited resources in the area, not all RRT modalities will be widely available. However, there is decreasing popularity of PD in AKI. Recent evidence has shown comparable efficacy of PD to the other modalities.
5. Long-term outcome of tropical infections causing AKI is still lacking. However, based on current evidence, there are favorable outcomes in leptospirosis- and malaria-associated AKI.

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