



Acute Kidney Injury in the Tropics: Epidemiology, Presentation, Etiology, Specific Diseases, and Treatment

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14.1 Introduction

The characteristics of acute kidney injury (AKI), including etiology and outcomes, are highly variable and are dictated to a great extent by the setting in which AKI develops. The etiology and outcomes of AKI developing in hospitalized patients (hospital-acquired AKI—HAAKI) are different from AKI developing in the community (community-acquired AKI—CAAKI), especially in the tropical climate [1]. Environmental and socioeconomic factors play a major role in human health and disease development in the tropics. A majority of AKI in the tropics is CAAKI, mostly as a consequence of the prevailing disease epidemiology and the variability in appropriateness of response by the local health system.

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14.2 The Tropical Ecosystem as a Driver of Disease

Approximately 40% of world population lives in the tropics, defined geographically as area between approximately 23° on either side of the equator, where the sun is directly overhead at least once during the year. Tropical climate is characterized by high ambient temperature; some tropical regions receive heavy rains, while others get little precipitation. The rainy tropical ecosystem promotes the survival of pathogenic microorganisms outside the human host and is suitable for proliferation of parasites and vermin that cause disease or act as reservoirs, intermediate hosts, and vectors. On the other hand, water scarcity in the arid regions increases the susceptibility of kidneys to relatively minor insults. The tropics are home to a number of poisonous snakes and arthropods. Flooding of burrows in the rainy season forces snakes to come to the surface at a time when large numbers of workers are in the fields for planting or harvesting crops, leading to a spike in the incidence of bite victims. Seasonal variation in the incidence of AKI due to tropical infections and snake envenomation is a common feature throughout the tropics.

Quality of drinking water plays a major role in the pattern of kidney disease in the tropics. A number of conditions that are associated with AKI in the tropics (see below) can be causally linked to contaminated water. The leaching of

minerals and organic compounds into the fragile tropical soil during rains leads to waterlogging and contamination of fields [2] and also promote waterborne diseases. Transmission by direct contact and aerosols is also more likely because of overcrowding and poor living conditions in the tropics.

Tropical countries differ from those in temperate regions in socioeconomic terms as well. Despite occupying less than 10% of the land mass and only 20% of world population, countries in temperate regions account for 52% of the world's gross national product [3]. Almost all of the tropical countries are classified by the World Bank into low or low-middle income categories. The healthcare systems in the poor tropical countries exhibit several limitations in the form of limited and unevenly distributed medical resources, lack of specialized care, high costs, fear and suspicion of modern medicine, and continued reliance on traditional health systems. The harmful consequences are both secondary to denial or delay of appropriate treatment, and the use of potentially toxic ingredients of indigenous remedies is toxic that can lead to AKI.

The combined effect of a high disease burden and poor economic performance is reflected in the lower life expectancy and high infant and maternal mortality rates in tropical countries. Even after correction for the level of income, the infant mortality rate in the tropical zone is 52% higher and the life expectancy 8% lower than those in temperate zones [3]. Tropical regions also have high fertility rates, which result in a high proportion of children in the population but at the cost of fewer resources per child. Conversely, illness depletes household savings, reduces productivity, decreases learning ability, and leads to a diminished quality of life, thereby perpetuating or even increasing poverty [4].

Economic considerations prevent the implementation of technological solutions that might be feasible in affluent nontropical countries. For example, advanced and expensive treatments, such as continuous renal replacement therapy, are eschewed in favor of cheaper and less complex peritoneal dialysis, resulting in trade-off with efficiency, flexibility, and personalization.

14.3 Epidemiology of AKI in the Tropics

14.3.1 Incidence

Paucity of community-wide reports on AKI from tropical countries has hampered efforts to estimate its burden and compare the pattern, presentation, and outcome with that from other parts of the world. The available reports are single-center studies conducted at academic institutions, which may not be truly representative of the true characteristics of AKI, especially in rural settings. Patients are referred in advanced stages of illness, often with complications, and those developing AKI in rural communities may not reach hospitals at all. Most of the available studies have used different denominators to calculate the incidence of AKI or described single entities like “obstetric AKI” or “AKI due to leptospirosis.” The absence of uniform definitions and use of inconsistent terminology has added another layer of complexity. All this makes estimation of disease burden and accurate comparisons difficult.

AKI is recognized as the most common renal emergency in tropical countries. However, the reported incidence has been variable and in general lower compared to other regions. In 2013, the International Society of Nephrology started the *Oby25* (zero preventable deaths due to AKI by 2025) initiative, with focus on LMIC. A meta-analysis done as a part of this initiative included a large number of studies that have not been published in mainstream journals and provided the most comprehensive documentation yet of the incidence of AKI in different parts of the world (Table 14.1) [5].

An important finding from this meta-analysis was that with uniform definition and better

Table 14.1 Incidence of AKI from different regions of the world

Tropics		Other regions	
South Asia	7.5%	North America	22.3%
Middle Africa	23.5%	Europe	20.8–25.2%
East Africa	13.5%	Australia and NZ	16.9%
South America	31%		

reporting from the LMIC, the incidence of AKI in tropical countries no longer seems to be low, as had been reported earlier. In fact, in regions from where reports are gradually becoming available, the burden of AKI in hospitalized patients seems to be equivalent. Also, patients with more severe stages of AKI had high mortality, similar to other reports (42% and 46%, unadjusted odds ratio 12.5 and 19.7, respectively) [5]. The report confirmed the higher incidence of CAAKI in the developing countries, delayed presentation, and greater likelihood of not receiving RRT despite being indicated due to lack of resources and being discharged from the hospital to home, rather than to a step-down facility.

The International Society of Nephrology Oby25 Global Snapshot [6] provided a unique, though limited, picture of AKI around the globe. The snapshot provided significant insights into differences in epidemiology of AKI between countries in different socioeconomic categories and reaffirmed previous concepts about epidemiology of AKI in the low-income tropical countries. The distinguishing features of patients with AKI in LIC and LMIC were young age, low prevalence of preexisting CKD, presentation with more severe stages of AKI and relative prevalence of AKI associated with sepsis, obstetric complications, and animal envenomation. Lack of resources and inability to afford therapy meant that a significant proportion of patients could not receive dialysis despite being indicated. Although the overall mortality was higher, the survivors were more likely to show complete recovery from AKI in LMIC.

14.3.2 Setting of AKI

In most nontropical countries, AKI is encountered largely among patients already admitted in hospital, either with multi-organ failure in the intensive care units or after major surgical procedures. Tropical countries of Africa, South and Southeast Asia, and Latin America, however, encounter a double burden of AKI—both CAAKI and HAAKI. The characteristics of HAAKI encountered in ICUs of large urban

tropical centers are largely similar to the high-income countries, with relatively accessible sophisticated healthcare systems, even though these ICUs may also have patients with AKI secondary to tropical diseases. In rural areas, CAAKI secondary to diarrheal disease, envenomation from snakebite, leptospirosis, malaria, or obstetric complications predominate [6]. The rural healthcare infrastructure is usually inadequate with limited or no facilities for renal replacement therapy (RRT) and lack of specialized doctors. Hospitals that have infrastructure are overwhelmed with large number of patients, especially with seasonal surge of infectious diseases like leptospirosis.

14.3.3 Age and Sex

The mean age of patients with AKI in the tropics is 37–47 years, in contrast to mean of over 65 years in nontropical countries. Individuals with tropical CAAKI have few, if any, underlying diseases that might increase their AKI risk [7]. While there is no sex difference in the incidence of AKI from other regions, literature on tropical AKI consistently report lower incidence in females, with female/male ratio ranging from 1:1.5 to 1:5. This is unlikely to be a true difference and may be attributable to sociocultural factors with males accessing healthcare facilities more frequently than females. Of note is the consistently high prevalence of obstetric AKI.

14.4 Etiology of AKI in the Tropics and Comparison with Temperate Regions

Unlike AKI in high-income countries, AKI in the tropics is usually the predominant presenting feature following a specific condition (e.g., snakebite) or a specific infection (e.g., malaria), and not a part of a general multi-organ failure syndrome.

The causes of CAAKI in tropical countries can be broadly divided into those caused by

infections; animal, plant, or chemical toxins; and obstetric complications (Table 14.2). Some of these causes have been well characterized and studied, whereas for others, the numbers of affected patients are small and only a temporal association suggests a cause and effect relation-

ship. Reliable estimates of the importance of the different causes of AKI are difficult to make, as these vary from region to region. Diarrheal illness and malarial AKI are major public health threats in most tropical countries, whereas leptospirosis, typhus, and envenomation are the main

Table 14.2 Causes of acute kidney injury in the tropics

Vector-borne infections	Malaria (<i>Plasmodium falciparum</i> , <i>Plasmodium vivax</i> , or <i>Plasmodium knowlesi</i> , transmitted by <i>Anopheles</i> mosquito)
	Dengue fever (dengue virus, transmitted by <i>Aedes</i> mosquito)
	Scrub typhus (<i>Orientia tsutsugamushi</i> , transmitted by trombiculid mites)
	Hemorrhagic Rift Valley fever (RVF virus, transmitted by <i>Aedes</i> or <i>Culex</i> mosquitoes)
Direct infections	Leptospirosis (<i>Leptospira interrogans</i>)
	Hantaviruses, also known as hemorrhagic fever with renal syndrome (Puumala and Hantaan viruses)
	Zygomycosis
Diarrheal diseases	Viral diarrhea (rotavirus, Norwalk agent)
	Enterotoxigenic or enteroinvasive <i>Escherichia coli</i>
	Bacillary (<i>Shigella</i>) dysentery
	Cholera
Other infections	Melioidosis (<i>Burkholderia pseudomallei</i>)
	Typhoid (<i>Salmonella typhi</i>)
	Chlamydia (<i>Chlamydia trachomatis</i>)
	Legionellosis (<i>Legionella pneumophila</i>)
	Human immunodeficiency virus
Plant and fungal toxins	Herbal medicines
	Impila tuber
	Djenkol beans
	Marking nut
	Mushroom
	Star fruit and other oxalate-rich plants
	Plant-derived toxins used as insecticides and to kill fish
Animal poisons	Snakebites
	Wasp, hornet, and bee stings
	Spider bite
	Jellyfish sting
	Scorpion sting
	Carp gallbladder or bile
Chemical nephrotoxins	Ethylene glycol, propylene glycol
	Paraphenyldiamine
	Ethylene dibromide
	Copper sulfate
	Chromic acid
Environmental factors	Heat stroke
	Natural disasters
Obstetric complications	Postabortal sepsis
	Ante- and postpartum hemorrhage
	Preeclampsia
Other causes	Intravascular hemolysis resulting from glucose-6-phosphate 1-dehydrogenase deficiency

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causes of AKI in South Asia; malaria and indigenous herbal remedies are the most common causes of AKI in Africa; and leptospirosis, dengue fever, envenomation, and obstetric complications are the main causes of AKI in Latin American countries.

Knowledge of etiological factors is helpful in eliciting appropriate history and coming to a quick diagnosis. Certain facts like intake of toxic plants or indigenous medicines may be thought of as irrelevant and hence not volunteered, while others like a clandestine abortion may be even suppressed due to social or cultural reasons.

14.5 AKI Syndromes in the Tropics

CAAKI in the tropics can be part of a constellation of manifestations, presenting as specific patterns of AKI “syndromes” in the tropics, which help the clinician in deciding a diagnostic approach (Table 14.3).

- Fever—AKI syndrome due to tropical infections (fever + jaundice + AKI, fever + hemorrhagic manifestations + AKI)
- Envenomation and poisonings (including snakebite, illicit liquor, and industrial chemicals)
- Obstetric AKI
- AKI related to use of indigenous or herbal medicines

Table 14.3 Common differential diagnosis of tropical acute febrile illness with AKI

Pattern of organ involvement with tropical febrile illness	Differential diagnosis
Fever + jaundice	Leptospirosis, malaria, dengue, hantavirus, rickettsiosis
Biphasic fever + conjunctival suffusion + thrombocytopenia + transaminitis	Leptospirosis
Continuous fever + severe respiratory symptoms leading to ARDS	Hantavirus
Fever + severe myalgia + thrombocytopenia + acalculous cholecystitis	Dengue fever
Fever + maculopapular rash + “eschar”	Scrub typhus
Fever + splenomegaly + thrombocytopenia	Malaria
Fever + exposure to unpasteurized milk products	Brucellosis
Fever + diarrhea	Bacterial or viral gastroenteritis

14.5.1 Febrile Illness with Acute Kidney Injury

A large number of patients with tropical infections develop AKI in the setting of an undifferentiated febrile illness. In the absence of obvious evidence of common bacterial infections like respiratory tract infection or urinary tract infection, specific tropical infections need to be considered in the differential diagnosis of patients with AKI in the setting of acute febrile illness in the tropics or in travelers returning from the tropics. AKI is encountered in over 40% of these cases and increases the mortality and morbidity risk [8]. Upto 92% of patients hospitalized with AKI in a tertiary care hospital in India had fever from a tropical infection (Table 14.4).

AKI in the setting of tropical febrile illnesses can have additional manifestations related to other organ systems like the liver, nervous system, and heart, coagulopathy, and thrombocytopenia. Identification of these syndromes helps in narrowing the list of diagnostic possibilities. The

Table 14.4 Etiology of AKI in children in India [42]

Infections	92 (55%)
<i>Pneumonia</i>	24 (14%)
<i>Diarrhea</i>	13 (8%)
<i>Sepsis</i>	13 (8%)
<i>Dengue</i>	10 (6%)
<i>Scrub typhus</i>	3 (2%)
<i>Leptospirosis malaria</i>	1 (1%)
<i>Malaria</i>	1 (1%)
Acute glomerular diseases	28 (17%)
Underlying renal diseases	10 (6%)
Underlying cardiac diseases	8 (5%)
Envenomations	7 (4%)
Hemolytic uremic syndrome	6 (4%)
Drugs	2 (1%)
Others	13 (8%)

Table 14.5 Etiology of febrile illness with AKI [7]

Diagnosis	Number of cases (%)
Scrub typhus	188 (51.2)
Falciparum malaria	38 (10.4)
Enteric fever	32 (8.7)
Dengue	28 (7.6)
Mixed malaria	24 (6.5)
Leptospirosis	12 (3.3)
Spotted fever	7 (1.9)
Vivax malaria	6 (1.6)
Hantaan virus infection	1 (0.3)
Undifferentiated	31 (8.4)
Total	367

common differential diagnosis of tropical acute febrile illness based on organ involvement is summarized in Table 14.5.

14.6 Specific Diseases

14.6.1 Envenomation from Animal, Plant, or Chemical Toxins

Encounters with animals and insects are common in the tropics, due to their ubiquitous distribution; the nature of work of the inhabitants of the region, who are largely engaged in farming activities; and lack of sufficient protective gear. Envenomation following snakebite and insect stings accounts for a significant proportion of AKI in tropical countries. Usually the bite or sting is obvious, but it is important to consider this diagnosis even in the absence of overt history if the clinical manifestation are suggestive, because it is well known that snakebites can happen while the subject is asleep, or without the subject recognizing that she has been bitten by a snake, or made contact with a toxic plant. This is also important in the case of children with AKI (Table 14.6).

14.6.2 Snake Envenomation

There are more than 2000 species of snakes worldwide, of which approximately 450 are poisonous. It is estimated that out of the 2.4 million

Table 14.6 Animal, plant, and chemical toxins that can cause AKI in the tropics

Animal poisons	Plant and fungal toxins	Chemical toxins
Snakebites	Herbal medicines	PPD
Wasp, hornet, and bee stings	Impila tubers	Ethylene or propylene glycol
Spider bite	Djenkol beans	Bromide
Jellyfish sting	Marking nut	Chromium
Scorpion sting	Mushroom	Copper sulfate
Carp gallbladder or bile	Plant-derived toxins used as insecticides and to kill fish	
	Oxalate-containing plants	

people bitten annually by poisonous snakes, approximately 100,000 die. About 45% of these deaths are reported from India [9]. AKI is an important contributor of these deaths. An additional 400,000 suffer nonfatal severe health consequences, such as AKI, amputation, infection, tetanus, scarring, contractures, and other sequelae attributable to envenomation [10]. Most instances of snake envenomation occur in tropical parts of Asia, Africa, and Latin America [11].

About 12% of all venomous snakebites are complicated by AKI, nearly all of whom following bites by colubrids, elapids, or hydrophids (Fig. 14.1). The species of the snake and the quantity of venom injected determine the clinical manifestations. Viper bites are characterized by florid local swelling, blistering, pain, tender regional lymphadenopathy, hemolysis, bleeding, and hypotension. Sea snake venom is myotoxic, and affected individuals develop myalgia and muscle weakness. Oliguria can develop within a few hours after the bite, or may be delayed for 3–4 days.

AKI is multifactorial in origin, with direct tubular toxicity, pigment-mediated tubular injury secondary to intravascular hemolysis or rhabdomyolysis, disseminated intravascular coagulation, or endothelial injury being the major causative factors. Fluid losses secondary to gastrointestinal symptoms or local infections can also contribute.

Grossly, the kidneys are swollen and appears “flea-bitten” secondary to petechial hemor-



Fig. 14.1 Two common varieties of viper snakes that cause AKI in South Asia. (a) Saw-scaled viper (*Echis carinatus*) and (b) Russell's viper (*Daboia russelii*)

rhages. Histology shows acute tubular necrosis with intratubular pigment casts in 70–80% of patients, other lesions being thrombotic microangiopathy, mesangiolysis, interstitial inflammation, glomerulonephritis, vasculitis, and renal infarction. Acute cortical necrosis, the most severe form of AKI, is seen in approximately 20–25% of patients after a Russell's viper or Saw-scaled viper bite.

Management consists of wound care, administration of antivenom and supportive treatment. Early antivenom administration prevents or attenuates the development of hematological abnormalities or rhabdomyolysis and AKI. There is no consensus on the dose of antivenom or the duration of therapy. One approach in the case of hemotoxic bites has been to titrate the dose according to the whole-blood clotting time. Some recent studies, however, have shown that the outcomes are similar even with the use of a fixed lower dose of antivenom. Supportive measures include judicious volume replacement, inoculation with antitetanus immunoglobulin, and appropriate management of bleeding risk by the use of fresh frozen plasma as needed. Patients bitten by myotoxic snakes need aggressive fluid therapy and urinary alkalinization to prevent intratubular precipitation of myoglobin. Mortality from snakebite envenomation is estimated to be up to 35%. A substantial proportion, especially those with patchy or diffuse cortical

necrosis and thrombotic microangiopathy, is left with varying degrees of renal insufficiency.

14.6.3 Insect Stings

Insects like honeybees, wasps, yellow jackets, and hornets are common in the tropics, and hence stings from these insects are also encountered not infrequently. AKI typically results in individuals who sustain multiple stings from a swarm of insects like honey bees or wasps, resulting in injection of a large dose of toxins. Kidney injury is usually secondary to hemolysis or rhabdomyolysis, though direct toxicity has also been proposed. Less commonly, AKI has been described following isolated stings secondary to anaphylactic reactions or thrombotic microangiopathy [12]. Apart from AKI, proteinuria and nephritic and nephrotic syndromes have also been reported after insect stings [13–15]. The diagnosis is usually obvious. Management is largely supportive and symptomatic, including short course of steroids, antihistamines, fluid replacement, and RRT if necessary.

14.6.4 Obstetric AKI

AKI related to complications of pregnancy (obstetric AKI) has been all but eliminated from developed nontropical economies due to system-

wide improvements in healthcare delivery. In contrast, obstetric AKI continues to be encountered in many tropical countries due to suboptimal antenatal care, frequent out-of-hospital childbirth, and unsafe abortion practices.

Obstetric AKI shows a bimodal temporal distribution: the first peak, attributable to hyperemesis gravidarum and septic abortion, is seen in the first trimester. Preeclampsia, eclampsia, placental abruption, postpartum hemorrhage, and puerperal sepsis develop close to term or following delivery and account for the second peak of AKI in third trimester or in the immediate postpartum period. There is a significant variation, however, in the frequency and outcome of obstetric AKI in different parts of tropics. In India, the contribution of obstetric AKI declined from 22% of all cases of AKI in the 1970s to approximately 8% in the 1990s. This decline was attributed to legalization of abortion and improvements in antenatal care [16]. In other parts of the tropics, however, obstetric AKI continues to be prevalent and has a poor prognosis even today. Septic abortion is the cause of AKI in 52% of patients in Ethiopia [17], and in Argentina and Nigeria, gynecological and obstetric complications still account for about one third of patients with AKI [18–20]. In one hospital in Pakistan, of 100 patients with obstetric AKI seen over a 3-year period, over 90% needed dialysis, 7% died in hospital, and only 44% were off dialysis at discharge [21]. About 20% of all patients develop acute cortical necrosis, the most catastrophic variety of AKI. In recent years, atypical hemolytic uremic syndrome, secondary to genetic abnormalities in complement regulatory proteins, has been recognized in several cases of third trimester and postpartum AKI (Ramachandran R, unpublished). It is important to identify these cases because they respond well to eculizumab.

14.6.5 Indigenous Medicine and Herb Use and AKI

The use of indigenous remedies of herbal or animal origin is an integral part of traditional cultures in many parts of sub-Saharan Africa

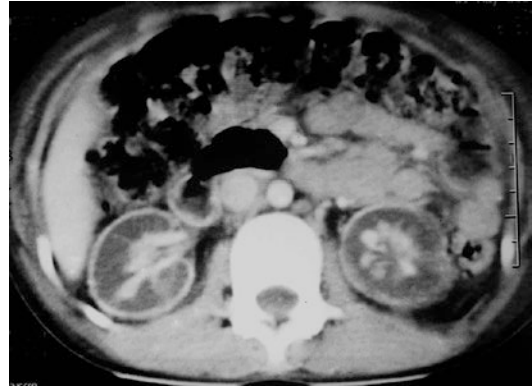


Fig. 14.2 Contrast-enhanced CT scan of a patient with acute cortical necrosis shows non-enhancing renal cortex bound on the outside by a rim of enhancing subcapsular region and on the inside by enhancing medulla

and Asia. AKI resulting from ingestion of plant, fungal, and animal nephrotoxins is common in countries in these regions. A variety of renal lesions including acute tubular necrosis, acute cortical necrosis, and interstitial nephritis have been reported [22]. Even some of the commonly ingested tropical plant foods can have toxic effects if consumed without proper preparation (Fig. 14.2). An example is the consumption of beans from the djenkol plant, a delicacy in several Southeast Asian countries [23]. Ingestion of a large amount of uncooked beans, especially in individuals with a low fluid intake, can cause oliguric AKI secondary to the intratubular precipitation of djenkolic acid crystals. The breath and urine of these patients have a characteristic, sulfurous odor, and the needlelike crystals can be seen in urine under light microscopy. Increased fluid intake and urinary alkalinization with sodium bicarbonate help to dissolve the crystals.

About 25–60% of all cases of AKI from medical causes in hospitals in sub-Saharan Africa are associated with the use of traditional herbal medicines. Such medicines are usually prepared under nonstandard conditions and are not tested for efficacy and safety, the ingredients are variable, and dosage and route of administration are often not standardized.

A large number of cases of AKI in Africa have been associated with use of extracts of impila tubers, which are taken either orally or as an

enema for their purgative and vermifugal effects [24]. Attractyloside, an alkaloid that inhibits ATP synthesis, is thought to be the active component. Symptoms appear 1–4 days after consumption and include abdominal pain, vomiting, seizures, oliguria, and jaundice. The mortality rate for impilarelated AKI is over 50%.

Potentially toxic substances like paint thinners, turpentine, chloroxylenol, ginger, pepper, soap, vinegar, copper sulfate, and potassium permanganate are often added to plant extracts in an effort to potentiate their effect [23].

The raw gallbladder or bile of sheep, freshwater carp, and grass carp are used for medicinal purposes in rural areas of the Middle East and South and Southeast Asia [25, 26] and can cause a syndrome of acute hepatic failure and renal failure. Oliguric AKI develops within 48 h and lasts 2–3 weeks. Susceptibility to AKI varies according to the species of fish, the amount of bile ingested, and patient-specific factors. An association has been found between the size of the fish and the severity of the toxic effect. The prognosis is usually good, and mortality has been described only in those who present late and already have multi-organ failure.

14.6.6 Paraphenyldiamine Nephrotoxicity

Paraphenyldiamine (PPD) is used in Africa, Middle East, and Indian subcontinent as a coloring agent, especially as hair dye. Clinical manifestations include cervicofacial edema, high colored urine, oliguria, edema, shock, and oliguric AKI. Direct toxicity, rhabdomyolysis, and hypovolemia contribute to AKI. PPD poisoning is the chief cause of AKI in some tropical African countries.

14.6.7 Infections

14.6.7.1 Malaria

Malaria continues to be a public health challenge throughout the tropical belt. The African region accounted for most global cases of malaria (88%), followed by the Southeast Asia (10%) and

the Eastern Mediterranean (2%). In 2015, there were an estimated 438,000 malaria deaths worldwide, with 90% in Africa [27]. Although *P. falciparum* infection accounts for most case of malaria-related AKI, *P. vivax* and *P. knowlesi* infections have also been reported to lead to AKI in recent years [28, 29].

AKI is seen in approximately 1–4% of all patients with *P. falciparum* malaria. The incidence increases to 60% in those with severe disease [27, 30]. Patients with severe parasitemia and children under the age of 5 years, pregnant women, and individuals with HIV or AIDS are at an increased risk [31, 32]. Mortality may be as high as 45%. About 70% of all deaths occur in children below the age of 5. The pathogenesis of malarial AKI is related to clogging of the microvasculature as a result of reduced deformability and increased stickiness of the parasitized erythrocytes that causes them to adhere to each other, other circulating cells, and the vascular endothelium.

The standard method of making a diagnosis is by demonstration of the asexual forms of the parasite in a thick finger-prick blood smear. Simple card tests that use antibodies to detect specific parasitic antigens allow quick diagnosis in the field where microscopy facilities or trained personnel are not available. The sensitivity and specificity of these tests are variable.

Artemisinin-based combination therapies are the recommended treatment for severe malaria with AKI [33]. Early effective antimicrobial treatment and timely renal replacement therapy are associated with improved survival and recovery of renal function in patients with malaria-induced AKI. A comparative study showed continuous renal replacement therapy to be better than peritoneal dialysis in malarial AKI.

14.6.7.2 Leptospirosis

Caused by the spirochete *Leptospira interrogans*, leptospirosis is the most widespread zoonosis in the world and an occupational hazard in fishermen, coal miners, sewage, abattoir, and farm workers throughout the tropics. Human infection occurs when organisms in contaminated water, soil, or vegetation enter abraded skin and exposed mucosa.

The disease presents with a biphasic febrile illness. Renal involvement is seen in the second phase and often presents with cholestatic jaundice and hemorrhagic manifestations (Weil's syndrome). AKI develops in 20–85% of cases and is oliguric in about half. Diagnosis is based on demonstration of anti-leptospira antibodies, either a single titer of >1:400 or a fourfold increase. Nucleic acid based testing has allowed identification of greater number of cases.

Renal injury is caused by direct invasion of the renal tissue by the organism and liberation of bacterial enzymes, metabolites, and endotoxins. Grossly, the kidneys are swollen and bile stained. The main light-microscopic lesion is a tubulointerstitial nephritis, with mononuclear cells and eosinophilic infiltration.

Leptospirosis is self-limiting, and mild cases recover with supportive treatment. Antibiotic therapy can shorten the duration of illness. The elderly and those with multi-organ involvement are at risk of adverse outcome.

Recent data suggests that leptospirosis may have long-term consequences for kidney health. In a community-based study, subjects with high leptospira antibody titers (indicating past infection) were more likely to show a decline in eGFR over a 2-year follow-up.

14.6.7.3 Scrub Typhus

Scrub typhus, caused by a gram-negative bacterium *Orientia tsutsugamushi*, is endemic in Asia and a grossly under-recognized cause of tropical febrile illness. The infection is transmitted to humans by trombiculid mites. A recent study [34] from India, employing a novel PCR-based diagnostic technique, showed that 24% of all patients presenting with unexplained febrile illness and/or multi-system involvement had scrub typhus. AKI was present in over 50% and was an important predictor of mortality. Vascular endothelial cell injury is thought to be the predominant mechanism of injury. Histology shows mesangial hyperplasia, acute tubular necrosis, or tubulointerstitial nephritis. Management entails a short course of doxycycline and supportive care. It has a fatality rate of 30% if untreated.

14.6.7.4 Diarrheal Diseases

AKI related to infective diarrheal diseases continues to be a major problem in tropical countries with poor sanitation, especially among the pediatric population and the elderly [35]. AKI related to diarrheal diseases is more frequent in rural areas and urban slums with inadequate provision of safe drinking water. The incidence increases during summer and rainy seasons. During the 1980s, 35–50% of all children who required dialysis for AKI in India had diarrhea-related AKI [36, 37]. The current incidence of diarrhea-related AKI requiring dialysis has declined to 8% as a result of the improved sanitation and widespread use of oral rehydration solutions [8].

Infective diarrhea may result from a variety of viral, bacterial, and protozoal infections. The clinical presentation provides clues to the identity of the causative pathogen. Early vomiting is a feature of rotavirus infection. Loose, watery stools indicate infection with enterotoxigenic *E. coli* or *Vibrio cholerae*. Fever, cramps, and tenesmus accompanied by bloody diarrhea suggest infection with *Shigella*, *Salmonella*, or enteroinvasive *E. coli*. Diagnosis requires stool microscopy, as with cholera or certain parasites and culture for other organisms.

Early and adequate fluid replacement using WHO-recommended oral rehydration solution (ORS) is the cornerstone of management. The ORS can be easily prepared at home by adding six (6) level teaspoons of sugar and half (1/2) level teaspoon of salt to 1 L of clean drinking or boiled water and then cooled (five cup full, with each cup about 200 mL). This will yield a solution with 75 mmol/L sodium, 65 mmol/L chloride, 20 mmol/L potassium, 10 mmol/L citrate, and 75 mmol/L of anhydrous glucose, with a resultant osmolarity of 245 mosm/L [38]. Intravenous rehydration might be required in patients with severe dehydration, persistent vomiting, or paralytic ileus. Hypokalemia may worsen during rehydration. The mortality rate associated with diarrhea-related AKI remains high in some tropical regions. In a study from Malaysia, the mortality rate was 2.1 per 1000 admissions [39].

In contrast, other tropical countries have practically eliminated diarrhea-associated AKI. An example is the nurse-led program developed by the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh, that has achieved a mortality rate of <1%.

14.6.7.5 HIV and AKI

HIV continues to be a major global public health issue and a leading global cause of infectious disease-related mortality, having claimed more than 34 million lives so far. In 2014, about 1.2 million people died from HIV-related causes [40]. The number of new HIV cases and AIDS-related deaths is declining, however. Between 2000 and 2015, new HIV infections and AIDS-related deaths fell by 35% and 24%, respectively. Approximately 36.9 million people were living with HIV globally at the end of 2014, 70% in sub-Saharan Africa [41].

AKI is encountered in over 50% of patients hospitalized with HIV infection [41]. Patients with HIV-AIDS are at high risk of AKI from various factors. Opportunistic infections, especially tuberculosis, volume depletion from chronic diarrhea due to intestinal parasites, the use of nephrotoxic antiretroviral drugs, and contrast agents for medical imaging increase the risk of AKI. HIV infection can give rise to AKI secondary to thrombotic microangiopathy.

AKI in patients with HIV has consequences beyond the acute episode, including an increased risk of cardiovascular events, end-stage renal disease (ESRD), and increased mortality [42]. Antiretroviral drugs used in highly active antiretroviral therapy (HAART), such as tenofovir and indinavir, can cause AKI. AKI in HIV-infected patients (in the HAART era) is associated with a sixfold increase in mortality [41]. Prevention of AKI requires attention to common risk factors like volume depletion and avoidance of nephrotoxic drugs, especially in individuals with preexisting CKD. Management entails maintaining a high index of suspicion, prompt correction of volume deficits, and attention to the list of medications.

14.6.7.6 Dengue Fever

Dengue fever is a mosquito-borne tropical viral infection caused by the dengue virus, often causing flu-like illness and occasionally causing severe disease with complications including AKI. The incidence of dengue has increased exponentially and more than half of the world population is at risk [43]. Dengue is found in tropical and subtropical climates worldwide, mostly in urban and semi-urban areas. The reported incidence of AKI in patients with dengue fever varies from 0.9% among Thai children [44] to 10.8% in reports from India [45]. Dengue was the cause of AKI in 4% of patients in an ICU in Brazil [46]. AKI usually develops in patients with severe disease (dengue hemorrhagic fever) and is frequently associated with hypotension, rhabdomyolysis, hemolysis, or sepsis. There is no specific treatment, and management is essentially supportive in nature. Prevention depends on effective vector control.

14.6.7.7 Post-Infectious Glomerulonephritis

Post-infectious glomerulonephritis (PIGN) is the result of an immunological process triggered by an infection afflicting the kidney, resulting in immune-complex-mediated glomerulonephritis. Though classically associated with streptococcal infection, PIGN can follow any bacterial, viral, fungal, or parasitic infection. Manifestation can be with asymptomatic urinary abnormalities, acute nephritic illness, hypertension, or rapidly progressive glomerulonephritis (more common in adults). While the incidence of PIGN has declined in the high-income countries, it continues to be a common condition in the tropical LMIC, where the burden of infection due to nephritogenic bacteria continues to be high. The burden of group A streptococcal infections was estimated to be 24.3 cases per 100,000 person-years in adults and 2 cases per 100,000 person-years in children in the developing countries [47], compared to 6 and 0.3 cases per 100,000 person-years, respectively, in developed regions. PIGN is primarily seen among children and

young adults in developing countries with a male preponderance of 2–3:1, while the patients in the developed world tend to be adults [48]. In a study from India, PIGN was identified as the cause in 86.7% of children who presented with nephritic illness [49] and PIGN accounted for 16.9% of AKI [50].

14.7 Prevention and Treatment

Community-acquired tropical AKI is largely preventable but requires public health policy initiatives and resources directed toward improvement of basic health needs, such as the provision of safe drinking water, improved sanitation, infection control through eradication of parasites and disease-carrying vectors, improvements in the conditions of farm workers, and the provision of good antenatal and obstetric care.

Vector control using an integrated vector management strategy is the most effective way to prevent transmission of vector-borne diseases. This is based on employing a range of interventions, such as rational use of pesticides and mosquito nets on the basis of local knowledge about vectors, disease determinants, and engagement with local communities and other stakeholders within a public health regulatory and legislative framework. Improving public awareness of the need for use of safe water, safe handling and use of pesticides and other nephrotoxins should be attempted by sustained campaigns in mass media.

Since most cases of tropical AKI are encountered in the community where trained healthcare personnel are scarce, nonphysician healthcare workers (NPHW) must be trained to look for early warning signs of AKI, identify those at highest risk for appropriate triage, and prompt referral of patients who need specialist care at secondary or tertiary hospitals. Availability of point-of-care tests will be helpful in this process. The few tests in development include those that measure salivary urea nitrogen or work on an algorithm based on urine color. Early institution of rehydration therapy may limit the sever-

ity of AKI. The ISN *Oby25* initiative is implementing a clinical trial that will test the hypothesis that NPHW-driven algorithmic triaging will lead to improved outcomes. Figure 14.3 shows a suggested algorithm for risk stratification and referral using locally appropriate point-of-care tests.

In addition to the severity of the disease, poor healthcare systems and the lack of infrastructure are believed to contribute to mortality and morbidity from AKI in the tropics. Even though HD is available in most tropical countries (with the possible exception of a few sub-Saharan African nations), facilities are concentrated in large cities that are often unable to cope with the huge demand for their services. Peritoneal dialysis is often resorted to, especially in remote areas [51] and for small children [52]. In view of the simplicity of technique and minimal technical requirements, the ISN, in association with the International Pediatric Nephrology Association, International Society for Peritoneal Dialysis, and the Sustainable Kidney Care Foundation, is implementing the Saving Young Lives project in tropical countries of Africa and Southeast Asia. Under this project, children with AKI are treated with PD [53].

14.8 Future Challenges

Tropical societies are likely to face major challenges to kidney health as a result of climate change and water scarcity. According to the UK-based risk analysis firm Maplecroft, the top 10 countries at “extreme risk” from climate change are all tropical countries.

Kidneys are likely to be particularly vulnerable to heat stress and the predicted reemergence of water- and vector-borne infectious diseases. Another area of concern is the evolution in the virulence of disease-causing organisms, as noted by emergence of kidney injury in vivax malaria and scrub typhus. This is compounded by emergence of antimicrobial resistance. Degradation of ecosystem and air and water pollution will increase the risk of exposure to environmental toxins that can cause AKI.

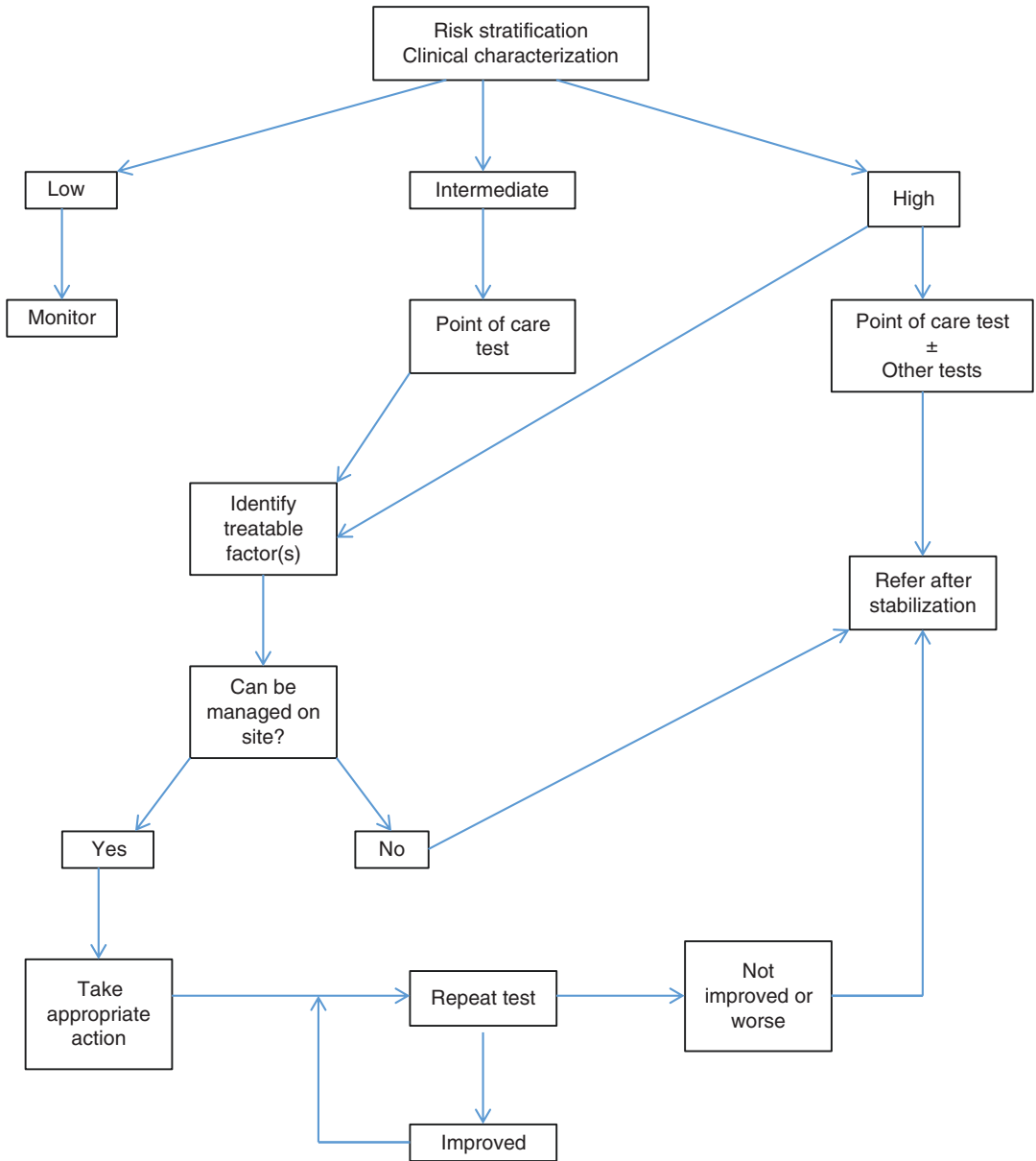


Fig. 14.3 A suggested algorithm for risk stratification, triaging, and referral of community-acquired tropical acute kidney injury

References

- Cerda J, Bagga A, Kher V, Chakravarthi RM. The contrasting characteristics of acute kidney injury in developed and developing countries. *Nat Clin Pract Nephrol*. 2008;4:138–53.
- Tiessen H, Cuevas E, Salcedo IH. Organic matter stability and nutrient availability under temperate and tropical conditions. *Adv Geoeol*. 1997;31:415–22.
- Sachs JM. Why tropical countries are underdeveloped. The National Bureau of Economic Research Working Paper Series [online]. 2001. <http://www.nber.org/w8119.html>.
- WHO. Health Topics [online]. 2011. <http://www.who.int/topics/poverty/en/>.
- Mehta RL, Cerdá J, Burdman EA, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet*. 2015;385(9987):2616–43.
- Mehta RL, Burdman EA, Cerdá J, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 global snapshot: a multinational cross-sectional study. *Lancet*. 2016;387(10032):2017–25.
- Jha V, Parameswaran S. Community-acquired acute kidney injury in tropical countries. *Nat Rev Nephrol*. 2013;9:278–90.
- Basu G, Chrispal A, Boorugu H, et al. Acute kidney injury in tropical acute febrile illness in a tertiary care Centre—RIFLE criteria validation. *Nephrol Dial Transplant*. 2011;26(2):524–31.
- Mohapatra B, Warrell DA, Suraweera W, et al. Snakebite mortality in India: a nationally representative mortality survey. *PLoS Negl Trop Dis*. 2011;5:e1018.
- <http://www.who.int/mediacentre/factsheets/fs373/en/>
- Kasturiratne A, Wickremasinghe AR, de Silva N, et al. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. *PLoS Med*. 2008;5:e218.
- Kumar V, Nada R, Kumar S, et al. Acute kidney injury due to acute cortical necrosis following a single wasp sting. *Ren Fail*. 2013;35:170–2.
- Abdulkader RC, Barbaro KC, Barros EJ, Burdman EA. Nephrotoxicity of insect and spider venoms in Latin America. *Semin Nephrol*. 2008;28:373–82.
- Cuoghi D, Venturi P, Cheli E. Bee sting and relapse of nephrotic syndrome. *Child Nephrol Urol*. 1988;9:82–3.
- Vikrant S, Patial RK. Acute renal failure following multiple honeybee stings. *Indian J Med Sci*. 2006;60:202–4.
- Chugh KS, Sakhuja V, Malhotra HS, et al. Changing trends in acute renal failure in third-world countries—Chandigarh study. *Q J Med*. 1989;73:1117–23.
- Zewdu W. Acute renal failure in Addis Ababa, Ethiopia: a prospective study of 136 patients. *Ethiop Med J*. 1994;32:79–87.
- Chijioko A, Makusidi AM, Rafiu MO. Factors influencing hemodialysis and outcome in severe acute renal failure from Ilorin, Nigeria. *Saudi J Kidney Dis Transpl*. 2012;23:391–6.
- Okunola OO, Ayodele OE, Adekanle AD. Acute kidney injury requiring hemodialysis in the tropics. *Saudi J Kidney Dis Transpl*. 2012;23:1315–9.
- Firmat J, Zucchini A, Martin R, et al. A study of 500 cases of acute renal failure (1978–1991). *Ren Fail*. 1994;16:91–9.
- Ali A, Ali MA, Ali MU, et al. Hospital outcomes of obstetrical-related acute renal failure in a tertiary care teaching hospital. *Ren Fail*. 2011;33:285–90.
- Luyckx VA, Steenkamp V, Stewart MJ. Acute renal failure associated with the use of traditional folk remedies in South Africa. *Ren Fail*. 2005;27:35–43.
- Segasothy M, Swaminathan M, Kong NC, et al. Djenkol bean poisoning (djenkolism): an unusual cause of acute renal failure. *Am J Kidney Dis*. 1995;25:63–6.
- Hutchings A, Terblanche SE. Observations on the use of some known and suspected toxic *Liliiflorae* in Zulu and Xhosa medicine. *S Afr Med J*. 1989;75:62–9.
- Centers for Disease Control and Prevention. Hepatic and renal toxicity among patients ingesting sheep bile as an unconventional remedy for diabetes mellitus—Saudi Arabia-1995. *MMWR Morb Mortal Wkly Rep*. 1996;45:941–3.
- Park SK, Kim DG, Kang SK, et al. Toxic acute renal failure and hepatitis after ingestion of raw carp bile. *Nephron*. 1990;56:188–93.
- <http://www.who.int/malaria/media/world-malaria-report-2015/en/>
- Naqvi R, Ahmad E, Akhtar F, et al. Outcome in severe acute renal failure associated with malaria. *Nephrol Dial Transplant*. 2003;18:20–3.
- Prakash J, Singh AK, Kumar NS, et al. Acute renal failure in *Plasmodium vivax* malaria. *J Assoc Physicians India*. 2003;51:265–7.
- Mehta KS, Halankar AR, Makwana PD, et al. Severe acute renal failure in malaria. *J Postgrad Med*. 2001;47:24–6.
- Mishra SK, Das BS. Malaria and acute kidney injury. *Semin Nephrol*. 2008;28:395–408.
- Jha V, Chugh KS. In: Ronco C, Bellomo R, Kellum J, editors. *Critical care nephrology*. Philadelphia: Saunders Elsevier; 2009. p. 850–6.
- WHO. Guidelines for the treatment of malaria. 2015. <http://www.who.int/malaria/publications/atoz/9789241549127/en/>.
- Kumar V, Kumar V, Yadav AK, et al. Scrub typhus is an under-recognized cause of acute febrile illness with acute kidney injury in India. *PLoS Negl Trop Dis*. 2014;8(1):e2605.
- Hayat A, Kamili MA, Samia R, et al. Peritoneal dialysis for adults with acute renal failure: an underutilized modality. *Saudi J Kidney Dis Transpl*. 2007;18:195–9.
- Choudhry VP, Srivastava RN, Vellodi A, et al. A study of acute renal failure. *Indian Pediatr*. 1980;17:405–10.

37. Chugh KS, Narang A, Kumar L, et al. Acute renal failure amongst children in a tropical environment. *Int J Artif Organs*. 1987;10:97–101.
38. WHO Drug information. Vol. 16, No. 2, 2002. <http://apps.who.int/medicinedocs/en/d/Js4950e/2.4.html>
39. Lee WS, Ooi TL. Deaths following acute diarrhoeal diseases among hospitalised infants in Kuala Lumpur. *Med J Malaysia*. 1999;54:303–9.
40. <http://www.who.int/mediacentre/factsheets/fs360/en/>
41. Wyatt CM, Arons RR, Klotman PE, et al. Acute renal failure in hospitalized patients with HIV: risk factors and impact on in-hospital mortality. *AIDS*. 2006;20:561–5.
42. Choi AI, Li Y, Parikh C, et al. Long-term clinical consequences of acute kidney injury in the HIV-infected. *Kidney Int*. 2010;78:478–85.
43. WHO Dengue and severe dengue Fact sheet. 2017. <http://www.who.int/mediacentre/factsheets/fs117/en/>
44. Laoprasopwattana K, Pruekprasert P, Dissaneewate P, et al. Outcome of dengue hemorrhagic fever-caused acute kidney injury in Thai children. *J Pediatr*. 2010;157:303–9.
45. Mehra N, Patel A, Abraham G, et al. Acute kidney injury in dengue fever using acute kidney injury network criteria: incidence and risk factors. *Trop Dr*. 2012;42:160–2.
46. Daher EDF, Silva Junior GB, Vieira APF, et al. Acute kidney injury in a tropical country: a cohort study of 253 patients in an infectious diseases intensive care unit. *Rev Soc Bras Med Trop*. 2014;47:86–9.
47. Carapetis JR, Steer AC, Mulholland EK, et al. The global burden of group a streptococcal diseases. *Lancet Infect Dis*. 2005;5(11):685–94.
48. Kanjanabuch T, Kittikowit W, Eiam-Ong S. An update on acute postinfectious glomerulo-nephritis worldwide. *Nat Rev Nephrol*. 2009;5:259–69.
49. Gunasekaran K, Krishnamurthy S, Mahadevan S, et al. Clinical characteristics and outcome of post-infectious glomerulonephritis in children in southern India: a prospective study. *Indian J Pediatr*. 2015;82(10):896–903.
50. Krishnamurthy S, Mondal N, Narayanan P, et al. Incidence and etiology of acute kidney injury in southern India. *Indian J Pediatr*. 2013;80(3):183–9.
51. Mohandas N, Chellapandian D. Value of intermittent peritoneal dialysis in rural setup. *Indian J Perit Dial*. 2004;6:19–20.
52. Kohli HS, Arora P, Kher V, et al. Daily peritoneal dialysis using a surgically placed Tenckhoff catheter for acute renal failure in children. *Ren Fail*. 1995;17:51–6.
53. Smoyer WE, Finkelstein FO, McCulloch MI, et al. “Saving young lives” with acute kidney injury: the challenge of acute dialysis in low-resource settings. *Kidney Int*. 2016;89(2):254–6.