Acute kidney injury due to tropical infectious diseases and animal venoms – a tale of two continents

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Running headline: Tropical diseases-associated acute kidney injury

Abstract

South and Southeast Asia and Latin American together comprise 46 countries and are home to about 40% of the world population. The sociopolitical and economic heterogeneity, tropical climate and malady transitions characteristic of the region strongly influence disease behavior and healthcare delivery. AKI epidemiology mirrors these inequalities. In addition to hospital-acquired AKI in tertiary care centers, these countries face a large preventable burden of community-acquired AKI secondary to tropical infectious diseases or animal venoms, affecting previously healthy young individuals. This manuscript reviews the epidemiology, clinical picture, prevention, risk factors and pathophysiology of AKI associated with tropical diseases (malaria, dengue, leptospirosis, scrub typhus, and yellow fever) and animal venom (snakes, bees, caterpillars, spiders and scorpions) in tropical regions of Asia and Latin America, and discusses the potential future challenges due to emerging issues.

Keywords: acute kidney injury; Asia; Latin-America; tropical infectious diseases; animal venom; emerging issues.

Introduction

The tropical regions of Asia (South and Southeast Asia), consist of 20 countries spread over 9.6 million km² and a population of 2.32 billion (33-58% urban). South and Southeast Asia have a GNI per capita (Atlas method) of about US$1,496 and US$ 9,602, respectively.[1,2] Latin America (LA) comprises 26 countries in approximately 19.2 million km^2, from Mexico and the Caribbean Islands in the north to Argentina and Chile in the south. Its population is estimated at 626 million (78% urban), with a GNI per capita of US$9,095.[3-6]

Covering more than 20% of the earth land surface, and home to about 40% of the world's 7.4 billion inhabitants,[7] countries of South and Southeast Asia and LA exhibit a striking heterogeneity in terms of sociopolitical, economic and developmental indices and variations in access to products and services, including healthcare. The governmental healthcare spending in most countries of these regions is low compared to countries in North America and Western Europe.[1,3] Private hospitals providing sophisticated care co-exist with severe lack of public sector health infrastructure, including deficiency of primary care.[8]

Disease epidemiology in Asia and LA, including that of AKI, reflects these inequalities. Characteristics of patients with AKI encountered in tertiary care hospitals in large cities are similar to their counterparts in high-income countries: most are elderly, critically ill with multiorgan failure, have chronic comorbidities, and the main AKI causes are ischemia, sepsis and nephrotoxic drugs. By contrast, AKI is frequently encountered in the community in smaller urban areas distant from large cities and in rural zones secondary to diarrhea, tropical infectious diseases, animal venoms, natural medicines and poor obstetric care, amongst previously healthy young individuals.[8-15] Most patients present late to the healthcare system, with advanced stage disease. Access to renal replacement therapy (RRT) is variable, due either to non-availability of resources or lack of affordability, and is not rare that a RRT

cannot be delivered despite being indicated.[8,14,15] There is paucity of epidemiological studies on this kind of community-acquired AKI, but recent meta-analyses have shown a high frequency and high early mortality for these patients.[8,15] The long-term consequences of surviving a community-acquired AKI, including morbidity, mortality, effects on quality of life and economic burden, are virtually unknown.

In this review, we will focus on the epidemiology, clinical picture, prevention, risk factors and pathophysiology of AKI associated with some important tropical diseases and animal venom in tropical regions of Asia and LA, and discuss potential challenges due to emerging issues.

Tropical infectious diseases-associated AKI

Despite systematic efforts at containment, infectious diseases continue to be important contributors to the burden of AKI in the tropics. Tropical AKI closely tracks the state of public health services, especially inadequate sanitary infrastructure, lack of preventive measures and poor access to health care. An estimate of the numbers affected is thwarted due to poorly organized systems of surveillance. Since patterns of organ involvement are not tracked, estimates of frequency of kidney involvement are either rough approximations or skewed towards those with advanced stage disease, since those patients are preferentially referred to tertiary care hospitals. Besides the high mortality and morbidity, these conditions impose large economic burden on countries with already limited resources. The escalating rate of tourism, work and business related travel and forced immigration due to poverty and wars makes it increasingly likely that pathogens and vectors once limited to a geographic area will spread to previously non-endemic regions. Tropical infections are often diagnosed late in non-endemic areas, with deleterious consequences.

A 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, such as respiratory or urinary tract infection, specific tropical infections need to be considered in the differential diagnosis. It is extremely important to recognize these syndromes not only because untreated infection may be fatal but also due the fact that the AKI incidence in population of febrile patients may be up to 41%. Patients can have additional manifestations related to other organ systems, such as liver, nervous system, or heart dysfunction, coagulopathy and thrombocytopenia. Identification of these syndromes helps in narrowing the list of diagnostic possibilities. The common differential diagnosis of tropical acute febrile illness based on organ involvement is summarized in Table 1.

We will discuss some important tropical infectious diseases associated to AKI below (summarized in table 2).

Malaria

A mosquito-borne disease transmitted by the bite of infected females *Anopheles* mosquito, malaria is caused by protozoans of genus *Plasmodium*. The global effort in combating malaria has resulted in an 18% decline in the number of cases worldwide over the last 15 years. Still, there were 214 million cases and 438,000 deaths worldwide due to malaria in 2015. Children < 5 years accounted for about 70% of all deaths. Approximately 3.2 billion individuals in 95 countries, including all South and Southeast Asian countries and most LA countries were at risk of malaria in 2015.[16,17] South and Southeast Asia accounts for approximately 10% of the world burden of malaria, and had about 19.5 million cases and 29 thousand malaria-related deaths in 2015.[18] In the American continent, malaria is endemic in 21 countries and approximately 20% of the population is at risk of infection. In 2014, 389,390 confirmed cases and 87 malaria-associated fatalities were reported to the Pan American Health Organization. Brazil presently is responsible for 42 % of all cases reported in LA. Transmission remains entrenched in the Amazon Basin, which accounts for 99.5 % of the country's malaria load.[19] Severe malaria, associated with high level of parasitemia (>5 %) is associated with dysfunction of major organs, and is a medical emergency.[11]

AKI develops following infection with *P falciparum*, *P vivax* and *P knowlesi* and more rarely after *P. ovale* infection.[20-24] The frequency varies from 1 to 4% in all patients, and goes up to 60% among those with severe disease.[20,25] Recent data suggest change in disease behavior, with a rise in the frequency of malaria-associated AKI from 4.7% in 1983-95 to 17% in 1996-2008 in certain regions.[26] Older reports described AKI as a complication of *falciparum* infection, but recently AKI has been increasingly reported in association with *vivax* in SA and LA and *knowlesi* in Southeast Asia.[27] While some of these discrepancies are likely due to

different AKI definitions used, possible changes in virulence of the causative protozoa must be considered. Severe parasitemia, age < 5 years, pregnancy, HIV infection, shock, hepatic involvement, acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC) have been identified as risk factors for development of malaria-associated AKI.[13,23,28,29] Whereas previous literature emphasizes severe AKI, with oliguria and need for RRT, cases with earlier stages of AKI are being increasingly reported.[22,24]

Factors implicated in the pathogenesis of malaria-associated AKI include vascular obstruction by infected erythrocytes, generation of reactive oxygen species, immune complex deposition, hypovolemia, [28] and systemic inflammation[30].[31] Renal histology usually shows acute tubular necrosis (ATN), but cortical necrosis (CN), thrombotic microangiopathy, and glomerulonephritis have also been described.[22,32-36] AKI increases mortality risk and length of hospitalization.[23] Lethality might be up to 45%[28], and has been associated with disease stage, severity scores, inotropics and ventilator support.[22] In children, DIC, jaundice and parasitemia were associated with mortality.[37] Prompt diagnosis, early antimalarial treatment, timely initiation of RRT and supportive therapy were associated with improved outcome and recovery of renal function in patients with malaria-induced AKI.[22,38,39]

Leptospirosis

The world's commonest zoonosis is caused by spirochetes of the genus *Leptospira*, and is endemic in large parts of Asia and LA. Humans are infected accidentally when the organisms shed in urine by the natural vectors (rodents, dogs, pigs, cattle, horses) enter the circulation through broken skin or mucosal membranes exposed to contaminated water or soil. Outbreaks occur after floods, hurricanes and earthquakes. Leptospirosis is an occupational hazard for farmers, pet traders, veterinarians, rodent exterminators, slaughters, garbage

collectors and sewer workers, since they are more likely to be exposed to contaminated material.[40-42]

The actual burden of leptospirosis is likely underestimated, since its diagnosis is often missed or mistaken due to the nonspecific nature of clinical presentation.[40,43] There are an estimated 1.03 million cases worldwide with 58,900 deaths annually, about half amongst young adult males (20 to 49 years). SA and tropical LA carry the highest morbidity and mortality burden.[44] A recent increase in disease frequency has been described in both Asia and LA.[41,45]

The clinical manifestations are variable, with most patients developing minor flu-like illness, headache, myalgia, nausea, vomits, skin rash and/or conjunctivitis. [40-42] Electrocardiographic abnormalities were described in almost 60% of hospitalized patients.[46] Other findings include hepatosplenomegaly, jaundice, and hemorrhages. Weil syndrome is the name attached to its most severe multisystemic presentation that includes ARDS, diffuse alveolar bleeding, pulmonary edema, hepatic failure and AKI.[40,41] Kidney involvement is practically universal, since the spirochetes infiltrate renal tissue. Urinary electrolyte wasting can lead to hypokalemia and hypomagnesemia.[40,41,47] AKI, usually non-oliguric and frequently accompanied by hypokalemia, is seen in 40 - 87% cases. Tubular disorders precede the decline in glomerular filtration rate (GFR).[48-50] Data on risk factors for AKI are scarce. In an outbreak in Philippines, duration of illness before admission, elevated baseline serum creatinine and thrombocytopenia were independent risk factors for AKI.[42] A multicenter study showed that urinary and plasma NGAL levels were elevated in leptospirotic patients who developed AKI as compared to those with preserved renal function.[51] AKI etiopathogenesis is multifactorial, including direct action of the bacteria on renal tissue, hypovolemia, hypotension, rhabdomyolysis, hyperbilirubinemia, and spirochete membrane proteins-induced glycocalyx and endothelial injury [40,51-53] Tubular dysfunction has been related to inner medullary collecting duct vasopressin resistance, proximal tubular sodium

and water tubular transporters and α-Na-K-ATPase decreased expression, and enhanced Na-K-2Cl cotransporter expression.[41,54] Renal histology shows interstitial nephritis, ATN and vasculitis.[40,54] Presence and severity of AKI and oliguria are associated with mortality[43,49,55-57]. Data on long-term outcome after AKI are rare. A study from Sri Lanka found that 9% of patients had developed stage 3 chronic kidney disease (CKD) one year after an episode of leptospirosis-associated AKI.[58] A community-based study showed that individuals with previous leptospira exposure had lower GFR and a higher frequency of CKD than those without leptospira exposure. Multivariable analyses confirmed the association between leptospiral infection and lower GFR.[59] A study from Brazil assessing patients with leptospirosis-associated AKI found that the creatinine clearance recovered three months after discharge, but the abnormal fractional excretion of potassium and urinary concentration capacity persisted. After six months, only urinary concentration ability remained impaired.[60] The mainstay of treatment is antibiotics of the penicillin group, but azithromycin, chloramphenicol, doxycycline, and cephalosporins have also been used. Patients can recover spontaneously with adequate supportive care, including fluid management and ventilatory support, and the actual benefits of antibiotics in leptospirosis remain unproved.[40,41,61,62] Early protective ventilatory support, pulse of corticosteroids and extra corporeal membrane oxygenation have been anecdotally used in severe leptospirosis complicated by pulmonary hemorrhage.[63-65] Early daily hemodialysis reduced mortality of severe leptospirosis in a series of Brazilian patients.[66]

Dengue

A viral disease caused by RNA arbovirus of the genus *Flavivirus* (family *Flaviviridae*), dengue is transmitted by female mosquitos of the genus *Aedes, aegypti* and *albopictus*. Four serotypes of dengue virus cause the disease and a new serotype was recently discovered in Malaysia.[67-69] Dengue has emerged as a worldwide public health problem, and is an example

of global dissemination of the vectors and their ability to adapt in domestic environments secondary to increased human mobility, climate changes and the unplanned urban growth.[67,68] Recent studies assessed the number of people at risk at about 4 billion in 128 countries,[70] and put the number of annual infections at 390 million, more than three times the World Health Organization (WHO) estimate,[71] with an projected annual cost of US$8.9 billion.[72] Southeast Asia records about 2.9 million dengue episodes and 5,906 deaths annually, with a yearly monetary burden of $950 million.[73] The number of dengue cases in India doubled from 2014 to 2015, with almost 10-fold increase in some states.[74] Similar increases have been reported from Pakistan.[75] In 2015, South America had 2.3 million suspected cases, with 10,276 severe cases and 1,181 deaths.[76] As of April 2015, the Brazilian Ministry of Health had registered 1,254,907 notified cases of dengue, accounting for most of the disease burden in LA[77]. A probabilistic sensitivity analysis estimated that Mexico had about 139,000 symptomatic and 119 fatal cases annually (2010-2011), with an annual cost of $87 million related to the illness and a yearly disease burden of 65 disability-adjusted life years per million population.[78]

Dengue can be asymptomatic or present as a subclinical infection. The clinical forms of the disease are classified as dengue fever, dengue hemorrhagic fever without shock or with shock and expanded dengue syndrome.[79,80] Dengue fever (DF) is an acute illness, characterized by fever, headache, retro-orbital pain, myalgia, joint pain, nausea and vomiting, itchy cutaneous rash and, occasionally hemorrhagic manifestations. Secondary infection, i.e. a re-infection with a different virus serotype from the primary infection, can result in severe forms of the disease. These forms are characterized by thrombocytopenia, evidence of capillary leak, such as elevated hematocrit, hypoalbuminemia, serous effusions and by hemodynamic instability.

Renal involvement can manifest as AKI, dyselectrolytemias, proteinuria, hematuria, and hemolytic uremic syndrome.[68,81-88] AKI frequency varies from 0.9% in Thai children[89] to

30.7 % in Southern Indian adults.[90] Studies using new AKI criteria reported frequencies up to 14.2% by AKIN and 12.6% by RIFLE.[91,92] AKI has been described in all forms of dengue[93] and the risk factors include elevated liver enzymes, low serum albumin, decreased serum bicarbonate, coexisting bacterial or viral infection, sepsis, multiple organs dysfunction, inotropic drugs, older age, obesity, severity of dengue infection, rhabdomyolysis, diabetes mellitus, late hospitalization and nephrotoxic drugs.[92,94] Postulated pathogenetic factors include direct viral effects on renal tissue, hemodynamic instability, rhabdomyolysis, hemolysis, acute glomerular injury, and systemic inflammatory response syndrome.[68,94-97] Histology showed ATN, thrombotic microangiopathy and glomerulopathy.[98-101] AKI is consistently associated with longer hospital stay and increased mortality.[94,102-104] Management entails careful volume replacement and supportive care depending upon manifestations.[105] The use of parenteral corticosteroids for severe dengue is debatable, and recommendations for its use in AKI patients does not exist.[106] It is advisable to monitor serum creatinine-kinase phosphate levels for early diagnosis of rhabdomyolysis and institution of appropriate preventive measures.

Scrub typhus

Scrub typhus is caused by the bacterium *Orientia tsutsugamushi* (formerly *Rickettsia tsutsugamushi*), and is transmitted to humans by infected *Leptotrombidium* mites larva (chiggers). An estimated 1 billion people worldwide are at risk, and an estimated 1 million cases occur each year.[107] The disease is endemic in South and Southeast Asia. [108] There is only one documented case reported in South America.[109] Manifestations range from mild, asymptomatic disease to a severe, fatal illness. Findings include lymphadenopathy, skin rash, fever, myalgia, headache, gastrointestinal symptoms and cough. A typical eschar occurs in the site of the bite, but is not always present. Severe disease is characterized by ARDS, AKI, bleeding, coagulation disorders, meningoencephalitis and shock.[110-115]

Renal involvement is common. Urinary abnormalities such as hematuria, proteinuria, pyuria and presence of granular casts occur in 50-80% patients.[116,117] AKI is frequent, ranging from 20% to up to 60%.[90,100,112-119] The possible mechanisms of AKI are infiltration and direct effects of the bacteria on kidney tissue[120,121], intravascular hemolysis associated to glucose-6-phosphate dehydrogenase-deficiency[122], rhabdomyolysis[116,123,124] renal ischemia due to hemodynamic instability and vasculitis.[116] Histopathology shows ATN, interstitial nephritis and mild mesangial glomerulonephritis.[120,125-127] AKI has been consistently associated to higher short-term mortality.[115-117] Early and adequate administration of doxycycline promotes remarkable improvement in the majority of patients, including renal function recovery.[113,128]

Yellow fever

Yellow fever (YF) is caused by the YF virus (YFV), an arbovirus considered the prototype for the *Flavivirus* genus and *Flaviviridae* family, which is endemic in areas of Africa and South America. The vectors are blood-feeding mosquitos of the genera *Haemagogus* in South America and *Aedes* in Africa. Massive vaccinations practically eliminated the disease in North America and Europe, and reduced considerably its incidence in Central and South America and Africa. However, due the existence of an YFV cycling between forest mosquitos and wild non-human primate hosts in Africa and Americas, YF has not been totally eradicated. Thirty-four countries in Africa and 13 countries in Central and South America have areas endemic for YF. The burden of YF during 2013 was estimated as 84,000 to 170,000 severe cases and 29,000 to 60,000 deaths. Practically 90% of YF cases and deaths occur in Africa. The dissemination of the urban mosquito vector, *Aedes aegypti*, and the escalation in air travel brings the fear of the introduction of the YFV outside endemic regions, particularly in the unimmunized densely populated areas of Southeast Asia, as recently seen with the worldwide dissemination of Chikungunya and Zika virus.[129-133] YF might range from an asymptomatic or mild illness to a fulminating, life threatening, multiorgan disease. A large

number of cases experience a self-limited disease, characterized by high fever, bradycardia, chills, anorexia, headache, muscle and back pain and prostration. Fifteen to 25% of the patients develop the most severe form of the disease, with hepatic failure, jaundice, hemorrhagic diathesis, epigastric pain, vomits, shock and AKI. Death occurs in up to 50% of these cases. Survivors experience a long convalescent phase, with weakness and fatigue.[129-131, 134,135]

Although AKI is always mentioned as part of severe YF[129-131,135,136] information about the frequency, risk factors, and etiopathogenesis of YF-associated AKI are very scarce. Oliguria ensued after five to seven days in severe YF, and even earlier in African patients without jaundice or hepatic abnormalities.[137,138] Renal histology disclosed ATN.[135,139] The mechanisms causing AKI are obscure. Renal ischemia, intravascular coagulation, shock, bilirubin-induced tubular toxicity, YF virus direct effect on the kidneys and an enormous inflammatory cytokines release are possible mechanisms of AKI.[140-145]

Animal venom-induced AKI

Accidents caused by venomous animals, such as snakes and arthropods (bees, wasps, spiders and caterpillars) are a significant public health issue in several areas of tropical countries. AKI is one of the main effects of these venoms, and associated with high morbidity and lethality. We will review bellow the most relevant aspects of AKI associated to snakebite (Russell's viper, Bothrops and Crotalus) and venomous arthropods (bees, Lonomia caterpillars, Loxosceles spiders and scorpions) in SA and LA (summarized in table 3).

Snake Bite

Like several tropical infections, venomous snake bites have been categorized as a neglected public health issue, particularly in LA, Asia and Africa by the WHO.[146] Data on the global burden of human envenomation due to snakebite estimates 421,000 to 1,841,000 cases with

20,000 to 94,000 deaths per year. SA and LA contribute the largest number of cases and SA had the higher mortality.[147] Vulnerable populations, such as the economically disadvantaged and those living in rural communities are affected disproportionately.[148] Because the available epidemiological information is almost completely based on hospital data and likely to have missed victims treated in community healthcare systems, the actual numbers are likely much higher.[149]

Snake venoms have a complex chemical composition, consisting mostly of potentially toxic proteins and enzymes, carbohydrates, lipids, metals, biogenic amines, free amino acids and nucleotides. They have evolved evolutionarily as hunting weapons, and human bites are accidental.[150] Clinical manifestations depend on the type and inoculated venom dose, bite site, victim body size and medical intervention timeliness. They range from mild local symptoms to severe systemic envenoming, which may become apparent in a few hours.

AKI is one of the most important causes of death in patients bitten by snakes of the class Viperidae and Hydrophidae.[151,152] The majority of AKI cases is caused by Russell´s viper accidents in Asia and by snakes of the genus Bothrops and Crotalus in LA.[153-158] Snake venoms are concentrated in renal tissue within minutes and appear in urine within a few hours after inoculation.[159-161] Unless preventive measures are implemented promptly, early renal dysfunction occurs frequently (see table 2).[157,162-168]AKI can be severe, oliguric and dialysis dependent.[10,162,169,170] Associated clinical findings might include, depending on the offending snake, those related to local injury (figure 1), rhabdomyolysis, intravascular hemolysis, consumptive coagulopathy, myocardial injury, neurotoxicity, loin pain, hypopituitarism and systemic inflammatory response syndrome. [154,157,169-177] Although most patients recover renal function, AKI after snakebite has been associated with development of CKD in both adults and children.[178-180] and may aggravate renal dysfunction in agrochemical nephropathy.[181]

The most frequent renal histological abnormality found in snake venom-associated AKI is ATN.[169,182-185] A small but significant minority of cases develop acute CN or acute interstitial nephritis (AIN). CN has been described mainly following Russell's viper and Bothrops bites[182,184,186-188], and foresees a bleak renal prognosis. Bilateral and diffuse involvement is associated with irreversible renal failure. CN should be suspected when oliguria persists beyond two weeks and can be confirmed by renal biopsy or a contrast-enhanced CT scan (figure 2). Glomerular injury has also been described, and is manifested histologically as ballooning of glomerular capillaries, splitting of glomerular basement membrane, swelling of endothelial cells, and focal mesangial cell proliferation.[189]

Several pathogenetic factors contribute to AKI, including hemodynamics abnormalities, hemolysis, rhabdomyolysis, direct tubular toxicity, systemic inflammation, activation of coagulation pathway leading to glomerular deposition of microthrombi, oxidative stress, hyperuricemia, release of cytochrome C and induction of apoptosis in tubular epithelium.[170,183,185,190-203]

The most effective way to prevent AKI is early and adequate administration of antivenom[204]. A prospective study on AKI after Crotalus snakebite in Brazil showed that an interval of over two hours between the bite and antivenom administration raised the AKI risk 10-fold after correction for other factors.[162] Similar association between delay in the timing for receiving antivenom and AKI have been reported in retrospectives studies after Bothrops and Russell's viper bites.[205-207] In experiments with fresh isolated proximal tubules antivenom only prevent tubular injury when added to the median simultaneously with the venom.[190] Limited availability and perceived risk of side effects have prompted to research in alternative antivenom therapies, none of whom have shown any promise.[208,209] The available antivenom in Asia is usually a polyvalent form raised against the "Big Four" (*D. russelii, Naja naja,*

Echis carinatus and *Bungarus caeruleus*), which may lead to incomplete neutralization of toxins of Russell´s viper venom.[210-212]

Bees

Honeybees, hornets and yellow jackets use venom as a defensive weapon aimed to protect the hive against intruders. Venom components are melittin (50%), histamine, hyaluronidase, apamin, acid phosphatase and phospholipase A_2 A_2.[213,214] Few stings usually cause only pain and allergic reactions. However, multiple stings following attack by a swarm introduces large doses of venom into circulation, causing severe multisystemic effects, including hemolysis, rhabdomyolysis, coagulation, cardiac, pulmonary, hepatic and nervous system disorders, hypertension and AKI.[214- 218] Of particular note are the Africanized honeybees found in LA, generated because of interbreeding between African honeybees that escaped from a Brazilian facility and European honeybees. They are much more aggressive than their predecessors and caused a spike in the number of cases in the region. [214,219]

Cases of AKI associated with honeybee attacks have been reported in India[220-222] and LA.[219,223-231] The largest series describes 43 patients with Africanized honeybee venom-associated AKI in Colombia. The victims were typically men from rural areas, with approximately 900 stings per individual. Almost all presented with rhabdomyolysis and oliguric dialysis-dependent AKI, which developed within 48 hr. Mortality was 16.3%.[229] The probable mechanisms of AKI are renal vasoconstriction, direct proximal tubular cells toxicity, hemolysis, oxidative stress, systemic release of inflammatory cytokines and pigmenturia.[214,232,233] Experimental studies showed that the injury can be mitigated by the use of human antibody fragments binding melittin and phospholipase A_2.[234] The most frequent renal histology finding is ATN.[213,219,222,232,235] The morbidity and lethality of massive attacks has prompted the development of a hyperimmune equine serum antivenom against

Africanized honeybee venom, which was effective in protecting against rhabdomyolysis and hemolysis in mice; it is yet unknown if this antivenom will prevent AKI.[236] Plasmapheresis, aiming to remove venom and inflammatory mediators, was used with success in a patient with more than 2,000 Africanized honeybees stings.[231] CVVH has been used in patients with honeybee venom-associated rhabdomyolysis and AKI, and led to decrease in serum myoglobin levels in 24 hours.[237]

Lonomia caterpillars

Caterpillars of the genus *Lonomia* have as natural habitat the trees in the deep forests of LA. They have a body covered by bristles, which inject venom when the victim touches the caterpillar (figure 3).[213,238] Deforestation have caused migration of these animals close to human habitations, increasing the number of accidents.[239,240] The clinical picture of these accidents is characterized by burning at the contact site, headache, fever, vomiting and a bleeding diathesis, which might be life threatening.[213,241]

Lonomia venom-associated AKI has been reported mainly in Brazil.[242-245] Early antivenom administration in rats prevented *Lonomia* venom-induced hemorrhagic manifestations and increase in serum creatinine.[246] The probably mechanisms of AKI are direct nephrotoxicity, intravascular hemolysis, systemic and endothelial inflammatory pathway activation, hypotension, increased renal tissue expression of proteins involved in cell stress, inflammation, heme-induced oxidative stress, coagulation and complement system activation.[247-249] Renal histology have shown ATN, glomerular fibrin deposition and ischemia and tubular atrophy.[243,244,249] Development of CKD following *Lonomia* venom-associated AKI was described in five patients.[245,250]

Loxosceles

Spiders of the genus *Loxosceles* are distributed worldwide, including SA and LA. Five species (*Loxosceles rufescens, L laeta, L intermedia, L gaucho and L reclusa*) are mostly responsible for human envenomation, known as loxoscelism, a major public health problem in South America (especially in Brazil, Chile and Peru), and also described in India.[251,252] *Loxosceles* are well adapted to domestic environment, where they hide inside clothes, towels and bed sheets and bite the victim upon contact.[251,252] The bite may go unnoticed, and the first presentation (12-24 h after the bite) takes the form of painful indurated edema, erythema, ecchymosis and hemorrhagic blister, which frequently progresses slowly (72 hours) to local necrosis and ulceration (figure 4). In approximately half of the cases, the cutaneous injury progresses to a dry necrotic round scar with defined margins. About half the patients exhibit systemic features, such as rash, fever, pruritus, malaise, headache, nausea and vomit. [251,252] Up to 27% of the patients develop viscerocutaneous or systemic loxoscelism, which is more frequent in Peru, Chile and some areas of South Brazil, characterized by intravascular hemolysis, jaundice, coagulation disorders, thrombocytopenia, rhabdomyolysis, hypotension/shock and AKI. [213,251-254]

Loxosceles venom-associated AKI was described rarely in India.[255,256] In Brazil AKI was reported ranging from 3.3 to 6.4%. [254,257] Cases were also described in Chile[258,259] and Peru.[260] The risk factors associated with AKI are severity of hemolysis, and accidents caused by *L laeta*. The mechanism of AKI might be linked to direct venom nephrotoxicity, hemoglobinuria, myoglobinuria, renal vasoconstriction, and systemic inflammation.[213,253,257,261-263] Renal histology have shown pigment-induced ATN.[258,263,264] Antivenom is probably the most effective therapy against AKI, but its application is often delayed as the bite goes unnoticed.[265] There is one case report relating a successful treatment with plasma exchange in a child with severe systemic loxoscelism, including AKI.[266]

Scorpions

Scorpions are venomous arthropods, responsible for over one million of accidents worldwide.[267] Severe envenomation is a public health issue in parts of LA, South Asia, North Africa, and Middle East, [268,269] and in some countries, such Brazil, scorpion stings exceed the number of cases of snakebite. [270] The genera tityus (South America) and centruroides (Mexico and Central America) in LA and the mesobuthus in Asia (particularly India) are medically relevant.[268,270,271] Scorpion venom is a hunting and defensive weapon, composed by several toxins. The toxins responsible for most of the medically relevant effects of the venom are small polypeptides (α-toxins), which inhibit mammalian voltage-gated sodium channels causing prolonged depolarization.[268,272] Scorpion venom causes autonomic overactivity, and a massive release of vasoactive substances and inflammatory cytokines.[268,272] The clinical picture is dominated by signs and symptoms of excessive cholinergic and adrenergic activity, cardiac dysfunction, and neuromuscular excitation. Severe cases, more common in children, may evolve to pulmonary edema, multiorgan failure and death. [268-270,272,273] Stings by the *H. lepturus* in Iran cause cytotoxic features, including hemolysis. [268,]

The venom is cleared mainly by the kidneys and liver and concentrates rapidly and intensively in renal tissue.[274] However, scorpion venom-associated AKI is rarely reported, with the majority of cases described in Middle East, and few cases in LA and SA.[269,271,275,276] The mechanisms of renal injury are likely renal ischemia due to vasoconstriction, hemodynamic instability, rhabdomyolysis, excessive systemic inflammation, and direct venom nephrotoxicity.[269,271,272,277] Renal histology shows ATN, glomerular changes, interstitial infiltrate, TMA and CN. [269,272,276-279] A case-control study in Mexico suggested that scorpion accidents were associated with development of CKD in children.[280] Use of

antivenom partially decreased kidney venom concentration in a mice model, and has been associated with more favorable clinical outcome.[268,274]

Future challenges

Tropical regions of Asia and LA are likely to face major challenges to kidney health because of climate change and water scarcity. According to the U.K.-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 re-emergence of water- and vector-borne infectious diseases. There is evidence that virulence of disease-causing organisms is changing, as noted by emergence of kidney injury in *vivax* malaria and scrub typhus and control getting harder due to emergence of antimicrobial resistance. Degradation of ecosystem, air and water pollution will increase the risk of exposure to venomous snakes and insects that were hitherto limited to areas away from human inhabitation. This unexpected burden of tropical diseases will likely further stress an overloaded healthcare system leading to deterioration in outcomes. We need more research in order to better understand the impact of infection and venom associated AKI on the long-term risk of CKD. This is of particular relevance as an increasing number of CKD cases are described in relatively young individuals where the etiology cannot be determined.

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Figure legends

Figure 1. Hemorrhagic blister and tissue necrosis at the bite site 48 hours after Bothrops snakebite (Courtesy Dr. Carlos A. C. Mendes, Sao Jose do Rio Preto Medical School, Brazil).

Figure 2. A. Contrast enhanced CT scan of a patient with persistent anuria after bite by a Russell's viper shown acute cortical necrosis characterized by nonenhancing renal cortex bordered on the outside by capsular rim and inside by the enhancing medulla. B. Histological examination of renal biopsy shown necrosis of all elements of renal parenchyma (H&E x 440)

Figure 3. Lonomia obliqua caterpillars, with the body covered by bristles, which inject the venom when the victim touches the caterpillar. Note the perfect mimetics of the animal (Courtesy Prof. Elvino J. G. Barros, Rio Grande do Sul Federal University Medical School, Brazil).

Figure 4. Typical local injury three days after Loxosceles spider bite (Courtesy Dr. Carlos A. C. Mendes, Sao Jose do Rio Preto Medical School, Brazil).

Table 1. Common differential diagnosis of tropical acute febrile illness associated to AKI.

Clinical picture	Differential diagnosis
Fever + jaundice	Leptospirosis, malaria, dengue, yellow fever, hantavirus, rickettsiosis, acute hepatitis
Biphasic fever + conjunctival suffusion + thrombocytopenia + transaminitis	Leptospirosis
Continuous fever + severe respiratory symptoms leading to ARDS	Hantavirus
Fever + severe myalgia + thrombocytopenia + acalculous cholecystitis	Dengue
Fever + maculopapular rash + 'eschar'	Scrub typhus
Fever + splenomegaly + thrombocytopenia	Malaria
Fever + exposure to unpasteurized milk products	Brucellosis
Fever + diarrhea	Bacterial or viral gastroenteritis

ARDS: acute respiratory distress syndrome.

Table 2. Some characteristics of the main febrile tropical diseases associated to AKI in South Asia and/or Latin America.

	Malaria	**Leptospirosis**	**Dengue**	**Scrub Typhus**	**Yellow Fever**
Pathogen	*Plasmodium* protozoans	*Leptospira* spirochetes	*Flavivirus* RNA arbovirus	Bacterium *Orientia tsutsugamushi*	Yellow fever arbovirus
Vector	*Anopheles* mosquitos	Rodents, dogs, pigs, cattle, horses	*Aedes* mosquitos	*Leptotrombidium* mites larva	*Haemagogus* and *Aedes* mosquitos
Affected areas	SA and LA	SA and LA	SA and LA	SA	LA
AKI frequency	1 to 60%	40 to 87%	0.9 to 30.7%	20 to 60%	Unknown
Renal histology	ATN, CN, TMA, GN	ATN, AIN, vasculitis	ATN, TMA, GN	ATN, AIN, GN	ATN
Long-term CKD	Described	Described	Unknown	Unknown	Unknown

AKI: acute kidney injury; CKD: chronic kidney disease; SA: South Asia; LA: Latin America; ATN: acute tubular necrosis; CN: cortical necrosis; TMA: thrombotic microangiopathy; GN: glomerulonephritis; AIN: acute interstitial nephritis;

Table 3. Some characteristics of the venomous animals causing accidents associated to AKI in South Asia and/or Latin America

	Russell's Viper	Bothrops	Crotalus	Bees	Lonomia	Loxosceles	Scor
Phylum	Cordata	Cordata	Cordata	Arthropoda	Arthropoda	Arthropoda	Arthropoda
Class	Reptilia	Reptilia	Reptilia	Insecta	Insecta	Arachnida	Arachnida
Order	Squamata	Squamata	Squamata	Hymenoptera	Lepidoptera	Arenae	Scorpionida
Suborder	Serpentes	Serpentes	Serpentes	Apocrita	Glossata	Araneomorphae	Scorpiones
Affected areas	SA	LA	LA	SA and LA	LA	SA and LA	SA and LA
Venom effects	Local injury, hemolysis, rhabdomyolysis, coagulopathy, neurotoxicity	Local injury, coagulopathy	Neurotoxicity, rhabdomyolysis	Hemolysis, coagulopathy, rhabdomyolysis, heart, lung, and liver injury, neurotoxicity	Coagulopathy	Local injury, hemolysis, rhabdomyolysis, hypotension and shock	Autonomic overactivity dysfunction edema, neur excitation
AKI frequency	18.7 to 45 %	1.4 to 38%	10 to 33%	unknown	1.9%	3.3 to 6.4%	unknown
Renal histology	ATN, CN, AIN, GC	ATN, CN, AIN, GC	ATN	ATN	ATN, GC	ATN	ATN, CN,
Long-term CKD	Described	Unknown	Unknown	Unknown	Described	Unknown	Unknown

GD: geographic distribution; SA: South Asia; LA: Latin America; AKI: acute kidney injury; ATN: acute tubular necrosis; CN: cortical necrosis;

AIN: acute interstitial nephritis; GC: glomerular changes; TMA: thrombotic microangiopathy; CKD: chronic kidney disease.