

Community-acquired AKI in Asia: An Update

Vivek Kumar¹ and Vivekanand Jha,^{2,3,4}*

¹Department of Nephrology, Postgraduate Institute of medical Education and Research,
Chandigarh INDIA

²George Institute for Global Health, UNSW, New Delhi, INDIA

² George Institute for Global Health, University of Oxford, Oxford, UK

²Manipal Academy of Higher Education, Manipal, INDIA

***Address correspondence to : Professor Vivekanand Jha, George Institute for Global Health, 310-11 Elegance Tower, Jasola New Delhi 110025, India**

SUMMARY

Community acquired acute kidney injury (CA-AKI) is the dominant form of AKI encountered in the developing countries of Asia. Economic disparities, variations in access to healthcare services, geographic conditions, environmental risk factors and socio-cultural circumstances shape the causes and outcomes of CA-AKI. Infections, drugs, plant and chemical toxins, envenomations, and obstetric complications are common causes of CA-AKI. Previously healthy young individuals who often work outdoors in fields or farms and are exposed to wide variety of work-related or environmental risk factors for CA-AKI. Improving disease definitions, better data and evolving host-pathogen interactions have changed disease descriptions and presentations over the last 20 years. Amongst infections, while incidence of malaria has come down, the number of cases with dengue and scrub typhus have risen sharply. The recognition of AKI in relation to *Plasmodium knowlesi*, *Plasmodium vivax* and scrub typhus, leptospirosis in areas not traditionally considered at risk, association of infections with future development of chronic kidney disease and role of complement dysregulation in infection associated AKI are important new findings. Snake-bite related toxic envenomation continues to be important cause of AKI in some counties and is a neglected public health problem. On the other hand, significant decreases in the incidence of AKI related to acute diarrhoeal illness or obstetric causes are signs of hope. Coordinated efforts between administrative stakeholders, society and healthcare delivery services at all levels have the potential to propel research and improve outcomes in CA-AKI.

KEYWORDS

Acute kidney injury, epidemiology, Asia, community acquired infections

INTRODUCTION

Acute kidney injury (AKI), a term proposed by a multidisciplinary group of experts in 2007 to replace the erstwhile acute renal failure (ARF), is universally acknowledged to be a common, serious and under-recognized condition. AKI can occur in a variety of clinical settings, and is a predictor of short and long-term adverse outcomes.

Until the last quarter of the twentieth century, the ARF syndrome was encountered primarily following pathogenic events that occurred outside the hospital. Variouslly called acute Bright's disease and 'war nephritis', ARF was recognised in the early 20th century following pregnancy, burns, trauma, consumption of toxic agents, or operations on the kidneys. Publication of the classical 1941 paper on crush syndrome during the London Blitz of the Second World War by Bywaters and Beall, and the introduction of the term acute renal failure by Homer Smith in 1951, were other important milestones.

With increasing life expectancy and introduction of complex technology in medical care delivery, ARF started to be increasingly recognised in individuals who were already hospitalised for other reasons. This was paralleled by substantial reduction in occurrence of ARF in non-hospital settings in North America, Western Europe and Japan secondary to economic progress, improvement in public health and reduction in conflicts. This shift led to change in the way this syndrome was identified, from largely on the basis on the clinical context, to changes in markers of kidney function - serum creatinine and urine output, culminating in the 2012 Kidney Disease Improving Global Outcomes (KDIGO) criteria to define AKI.

Over time, it became clear that despite similarities in the time course and potential reversibility, AKI that developed in already hospitalised patients as a result of patient and healthcare exposure-specific factors (hospital-acquired AKI, HA-AKI) was different to the one in which a previously healthy person developed kidney injury due to external factors (community-acquired AKI, CA-AKI). CA-AKI is overwhelmingly encountered in developing countries, particularly amongst the disadvantaged populations, and has a huge impact on families, societies and national economies (Table 1). The response of the healthcare systems to issues related to social equity is also influenced by the societies' value systems. The understanding of these differences, in particular the sociocultural and economic determinants (figure 1), the potential of addressing these issues through population-level interventions and the resulting need of taking a system-wide approach involving stakeholders beyond the nephrology/physician community suggest the need of a different approach for CA-AKI.

Knowledge of the diversity of Asia is relevant to understanding the spectrum of CA-AKI. Besides the geographical, political, climactic, ecological, environmental, ethnic, socio-cultural, and economic variations; countries of Asia are going through rapid population and epidemiologic transitions; are at different levels of development; and have widely varying healthcare structures. With the exception of Japan, South Korea, Singapore and Hong Kong, all Asian countries are classified under the low and middle income groups by the World Bank.¹ The differences are impacted by regional conflicts, natural disasters, human conflicts, and the effects of climate change.

In 2008, we reviewed the burden, pattern and challenges associated with CA-AKI in Asia in the pages of *Seminars in Nephrology*.² In this paper, we provide an update on the understanding of CA-AKI, review new data from Asia and discuss future challenges.

The full understanding of CA-AKI is limited by the absence of a clear definition. Generally, patients who are admitted to hospitals with AKI or develop AKI within 24-48 hours of admission are regarded as having CA-AKI. Quite often, this ascertainment is not possible because baseline creatinine values are not available, and the diagnosis can only be confirmed retrospectively when the creatinine trajectory shows a decline from a previous high value.

As noted in the 2008 paper, large amount of the data on CA-AKI in Asia came from case reports, or individual referral center-based case series. Lack of population-based AKI registries, organized surveillance systems or referral data continue to thwart an accurate assessment of CA-AKI burden in Asia. Since patterns of organ involvement are not tracked in common illnesses in the community, estimates of frequency of kidney involvement are skewed toward those with advanced-stage disease, since those patients are preferentially referred to hospitals. The fact that majority of patients with AKI in even specialized centers have CA-AKI, suggests that the burden in community is likely to be even higher. A systematic review of reports published between 2004-12 suggested that the global pooled incidence rates for AKI were 21.6% and 33.7% in adults and children, respectively.³ The evidence base for this review had low proportional representation from Asia and included very few studies that clearly identified CA-AKI. The pooled incidence and mortality rates for AKI in Asia were reported to be 15.6% and 30.2%, respectively.³ Recently, the *International Society of Nephrology (ISN) 0by25 Global Snapshot study*⁴ found that 80% of the AKI in low and lower middle income countries (LLMICs) were CA-AKI, highlighting the need to address CA-AKI to bring about meaningful change in outcomes of AKI on a global scale.^{5,6} Pediatric data from this Global Snapshot study showed 55 times higher mortality from AKI in LLMICs as compared to high income countries (HIC).⁷

CA-AKI IN ASIA: WHY IS THE BURDEN HIGH?

Most of the CA-AKI in Asia is reported from the LLMICs. A complex interplay between geographical characteristics, environmental factors, and poor socio-economic circumstances drives the presentation and outcome of this condition.⁸ Environmental factors, such as high temperatures, humidity, rain and fragile soil support the persistence and propagation of microbes, insects, parasites, and pests in the tropical regions of Asia. The same combination of factors allows venomous snakes and stinging insects to thrive. Tropical plants, several of whom are rich in nephrotoxic compounds, are consumed during religious or social rituals or prescribed by local faith-healers for treatment of common ailments. Knowledge of these factors is fundamental to understanding CA-AKI in this region.

In a retrospective cohort study from Japan, the seasonality in hospitalized patients with AKI was mainly attributed to CA-AKI.⁹ This indirectly shows the association of environmental factors with CA-AKI. This exposure is particularly relevant for people living in rural areas who are critically dependent on agriculture for livelihood. Rains and flooding lead to water-logging and contamination of natural sources of drinking water, and increase the risk of water-borne communicable diseases. Working outdoor in fields without protection increases the risk of accidental snake bite or insect stings. Loose regulatory framework around availability of toxic compounds like pesticides increase the risk of accidental exposure as well as consumption for suicidal or homicidal purposes. Low income and limited resources impair the ability to seek treatment either because of unavailability or unaffordability. Social and cultural taboos promote reliance on unproven local treatments that can cause delays or even be harmful. Certain groups, like women, children and the elderly are particularly disadvantaged in terms of access to treatment.

CA-AKI IN ASIA: TRENDS AND CAUSES

Table 2 shows the etiological factors responsible for CA-AKI in Asia. Multiple mechanisms and risk factors can be present in a single individual. In a retrospective, cross sectional study done as two single-month snapshots in 2013 at 44 centers across China that enrolled 7604 patients with AKI admitted to hospitals, CA-AKI accounted for 54% of all cases.¹⁰ Pre-renal, intrinsic renal and post-renal (obstructive) mechanisms were identified in 49%, 27% and 12% cases.¹⁰ The commonest contributing factors were decreased renal perfusion and nephrotoxic drugs in 75% and 60% cases, respectively.¹⁰ There were regional differences - decreased renal perfusion was more common in northern regions whereas nephrotoxic drugs and sepsis were more common in Southern China.¹⁰ These data were from referral or specialist centers and hence, likely to be under-representative of true burden of CA-AKI. The exact etiologies were not reported. Infections, including acute diarrheal illnesses, drugs and obstetric complications are the leading cause of CA-AKI in South Asia.^{2,11-15} Single center studies suggest that CA-AKI constitutes almost 75-92% of all AKI cases admitted to hospitals in India.^{11,13,16} The average age of patients with CA-AKI is <50 years in India, in contrast to >60 years in China.^{10-12,17} In a single center study from India which compared CA-AKI over two time periods (1996-2008 versus 1983-95), CA-AKI secondary to acute diarrheal illness and obstetric complications decreased but those related to other infections and nephrotoxic drugs increased.¹⁸ In a retrospective cohort study that analyzed hospital admissions over 5 years between 2010-14 in Taiwan, annual rate of CA-AKI increased from 12.43 to 19.96 per 1000 hospitalized adults.¹⁹

AKI as is often encountered in the setting of an undifferentiated febrile illness with non-specific systemic symptoms e.g. bodyaches, nausea, malaise and lethargy, and variable involvement of nervous, respiratory, hepatic, renal, hematopoietic and other systems (Table 3). In a study of

367 patients with acute febrile illness from India, AKI was present in 41%.²⁰ Malaria, leptospirosis, dengue, enteric fever and viral hemorrhagic fevers are the common causes.^{17,20} It is often difficult to pin down the cause on the basis of clinical presentation alone. An accurate causal diagnosis is delayed because of lack of availability of diagnostic facilities or specific tests.^{20,21} An example is scrub typhus, which was recognized only recently as an important cause of community acquired acute febrile illness, once appropriate diagnostic tools became available.²⁰⁻²² Such patients are often treated empirically by a cocktail of drugs which imposes the additional risk of complications, including drug-induced AKI.

The mechanisms that can lead to renal injury (Table 4) include direct injury by the infectious agents, systemic effects of infection e.g. hypovolemic or septic shock, tubular injury due to hemolysis or rhabdomyolysis, microvascular injury due to sepsis-induced disseminated intravascular coagulation, and immunological injury related to drug use. Leptospirosis, scrub typhus and Hantaanvirus infection cause acute interstitial nephritis, acute tubular necrosis, or a combination of the two.²³⁻²⁶ Other viral and bacterial infections including Dengue hemorrhagic fever or enteric fever can cause acute glomerulonephritis. Fungi of the class Zygomycetes are angio-invasive and lead to renal infarction.²⁷ In addition to volume depletion, acute diarrheal illness due to Shiga (or Shiga like) toxin producing strains of *E Coli* and *S dysenteriae* can cause thrombotic microangiopathy (TMA). Inappropriate complement activation or complement dysregulation is considered central to the pathogenesis of this condition.^{28,29} Complement activation, possibly on a background of pre-existing genetic variations, has been proposed to be responsible for development of TMA in obstetric AKI, leading to acute cortical necrosis (ACN). Hypovolemia secondary to excessive sweating or gastro-intestinal losses, and poor intake secondary to decrease in appetite and nausea can lead to pre-renal AKI. Severe dehydration in neonates can lead to renal vascular thrombosis.³⁰

Widespread systemic inflammatory effects of infection can cause renal hypoperfusion due to microvascular shunting.³¹ Hemoglobinuria or myoglobinuria can develop in malaria, leptospirosis, dengue, or scrub typhus. Use of alternative remedies of unknown composition, often sourced from locally available plants, animal parts or soil, occasionally mixed with chemicals has been associated with AKI, presumably through direct renal tubular toxicity or by immune injury. Indiscriminate use of prescription drugs also causes AKI, often due to lack of awareness. An example is use of primaquine for malaria or dapsone for leprosy without first looking for red blood cell glucose-6-phosphatase dehydrogenase (G-6PD) activity status. Those deficient in the enzyme develop severe hemolysis and AKI. The ability to obtain nephrotoxic medicines without prescription, such as antibiotics or non-steroidal anti-inflammatory agents (NSAIDS) contributes to CA-AKI.

A number of morphologic forms of renal injury have been reported in tropical infections associated AKI (Table 5). Multiple mechanisms might be operational in the same patient, leading to expression of variable morphologic forms.

The following section provides updates over our 2008 paper on CA-AKI related to specific disease entities in Asia.

Malaria

Malaria caused by protozoan *Plasmodium* and spread by Anopheles mosquitoes, is one of the commonest vector borne diseases that cause AKI. After Africa, South-East Asia sees the largest number of malaria cases.³²

Global malaria incidence and mortality fell by 21% and 29%, respectively between 2010 and 2015,³² and WHO declared Sri Lanka and Maldives malaria free in 2016. Bhutan, DPR Korea, Nepal, Sri Lanka and Thailand have reported decreases in the number and incidence rate of microscopically confirmed cases of $\geq 75\%$ since 2000. Bangladesh recorded a decrease of 69% in malaria case incidence between 2000 and 2011 and achieved a decrease of 75% by 2015.^{32,33} Despite these impressive advances, 212 million new cases and 429,000 deaths were attributed to malaria globally in 2015.³² In 2011, 2.15 million parasitologically confirmed malaria cases were reported in the WHO South East Asia region, with 3 countries accounting for 95% of confirmed cases: India (61%), Myanmar (22%) and Indonesia (12%).

Recent years have seen emergence of evidence from Asia that suggests *Plasmodium* species other than *falciparum* cause AKI. Multiple studies have documented AKI in patients with *P. vivax* infection (previously considered benign), with prevalence varying from 1-36%.^{34-36,37,38,39} Severe forms of AKI, such as crescentic glomerulonephritis, acute cortical necrosis and thrombotic microangiopathy have also been reported. Delayed diagnosis, anaemia, severe AKI, shock, acute respiratory distress syndrome, need for ventilatory support, raised serum transaminases and metabolic acidosis are associated with adverse outcome.

Recent reports have documented human malaria and AKI following infection with *P. knowlesi*, a parasite of old world monkeys that has now become a full blown zoonotic human parasite following host-switch. The initial reports came from Malaysia⁴⁰ but it has since been described with increasing frequency from Cambodia, Indonesia, Myanmar, Philippines, Singapore, Thailand and Vietnam.^{41,42} In fact, *P. knowlesi* malaria is now considered the commonest indigenous form of malaria in Malaysia, and the one more likely to lead to heavy parasitemia and severe disease.^{41,42} In one study, severe malaria occurred in 38 of 130 (29%) patients

with *P knowlesi*, 13 of 122 (11%) with *P falciparum*, and 7 of 43 (16%) with *P vivax*.⁴³ AKI has been described in about 55% of cases with *P knowlesi* malaria, a figure higher than those described for other species.⁴⁴ *P knowlesi*, however, is exquisitely sensitive to artesunate therapy.

Understanding the epidemiology of malaria and AKI has also been impacted by changed case definitions. The World Health Organization (WHO) provided an operational definition for use in the field, in which renal involvement qualifying for diagnosis of severe malaria was defined as serum creatinine >3 mg/dL or blood urea >122 mg/dL.⁴⁵ However, in institutional settings, most current AKI definitions and classification criteria (such as KDIGO or AKIN) have been used. Using the risk, injury, failure, loss, and end-stage renal failure (RIFLE) criteria, 73.9% of patients with severe *P falciparum* malaria were diagnosed as having AKI in Northern Thailand.⁴⁶

There are some new developments in treatment. Tafenoquine has emerged as a single dose alternative to primaquine, and received US FDA approval in 2018.^{47,48} Other new drugs, DSM265 and AQ-13 have shown promise in Phase 2 studies but must undergo further trials before being introduced into clinical practice.^{49 50} At community level, vector control is an important strategy to control spread of malaria. Resistance of mosquitoes to insecticides and resistance of *P falciparum* to artemisinin are two major concerns that can derail the progress achieved so far.³²

Leptospirosis

Leptospirosis, the commonest zoonosis in the world, continues to be of great public health importance in Asia. Globally, over 1 million estimated cases and 60,000 deaths are reported

every year.^{51,52} South-East, South and East Asian regions have higher burden of disease. Interestingly, cases have also been reported from high-income Asia-Pacific regions,⁵¹ especially in farmers after recreational exposure to freshwater environments, or upon return from tropical areas. Leptospirosis outbreaks with AKI, related to indigenous exposure to rats, have been reported in urban areas in Japan and South Korea.^{53 54}

Recent data shows that the risk for human leptospirosis might be greater than previously understood. Since rodents are the main reservoir hosts for *leptospira*, exposure to rats was thought to be essential for development of human leptospirosis. Evidence has recently emerged from Sri Lanka that other semi-domestic farm animals such as cattle and buffalo may act as important maintenance or accidental hosts, and exposure to these hosts might pose a zoonotic risk.⁵⁵ *L. interrogans* and *L. borgpetersenii* species are the most prevalent strains, and the main causative agents for human leptospirosis in South-East Asia.⁵⁶ The different habitat requirements for the two, (humid habitats, as in rice fields and forests for *L. interrogans*, and both humid and dry non-flooding habitats for *L. borgpetersenii*),⁵⁶ suggest that the risk for human infection is not restricted to wetlands but may extend to other settings also e.g. working in forests, hunting etc.⁵⁶ This was confirmed in a recent systematic review that showed that livestock contact, poor sanitation and behavioral risk factors like walking barefoot, uncovered wounds and collecting firewood were also associated with leptospirosis risk.⁵⁷

Finally, recent data suggests that leptospirosis might play a role in the development of chronic kidney disease (CKD). Yang et al⁵⁸ evaluated the correlation between previous *leptospira* exposure as determined by antibody titers using microscopic agglutination test (MAT) and eGFR in 3045 participants as part of a multistage sampling survey for CKD. Individuals with evidence of past exposure exhibited a lower eGFR (98.3 ± 0.4 vs 100.8 ± 0.6 ml/min per 1.73

m2, $P < 0.001$) and a higher prevalence of CKD (14% vs 8%). They also measured titers in 88 subjects in a leptospiral endemic town and followed them up for 2 years. Subjects with a MAT titer ≥ 400 showed a decline in eGFR, suggesting that past or subclinical human exposure to leptospira may be linked with CKD. It has been speculated that leptospirosis may contribute to CKD of unknown etiology reported in Asia.⁵⁹

In contrast to these reports, the prevalence of leptospirosis and AKI has drastically come down in the south Indian states of Tamil Nadu and Kerala, where it was the main cause of AKI till 10 years ago. This has been attributed to vector control, and improved sanitation and working conditions for rural farmers (Gopalakrishnan N, personal communication). Availability of molecular tests has improved the accuracy of diagnosis.

Dengue

The prevalence of dengue, a viral infection transmitted by *Aedes aegypti* mosquitoes has risen dramatically in Asia over recent years.⁶⁰ AKI develops in 10-36% cases^{61,62,63}, and is an independent predictor of mortality.⁶³ Subclinical urinalysis abnormalities are more common.⁶¹ Etiologic factors include shock secondary to increased vascular permeability, rhabdomyolysis, hemolysis, thrombotic microangiopathy, infection induced cytolytic glomerular and tubular injury and immune mediated damage.^{61,64,65,66,67} In endemic areas, dengue fever should be suspected in kidney transplant recipients who present with fever and acute kidney injury. Treatment is supportive, and vector control using public health measures are important.

Scrub typhus

Scrub typhus, caused by the rickettsial organism *Orientia tsutsugamushi* and transmitted by trombiculid mite, has re-emerged and become endemic in parts of Asia known as

‘tsutsugamushi triangle’ that runs from Northern Japan and Eastern Russia in the north to Northern Australia in the south and to Pakistan in the west.⁶⁸ In the mainland China, the number of cases increased 13-fold between 2006 and 2014.⁶⁹ Scrub typhus has recently been documented to be an important cause of acute febrile illness in India and is being seen in increasing numbers.^{21,70-72} Climate change, deforestation, urbanization and widespread use of drugs like penicillins that are ineffective against rickettsiae have been suggested as causal for re-emergence of this disease. Lack of awareness and non-availability of diagnostic tests are responsible for underdiagnosis.

AKI is common in scrub typhus, with frequency ranging from 36-82%,^{21,73} and is an independent predictor of mortality.²¹ Pathogenetic factors include impaired renal perfusion secondary to volume depletion or increased vascular permeability, direct tubular toxicity, rhabdomyolysis, interstitial nephritis, immune mediated glomerular injury and thrombotic microangiopathy.^{21,74} Doxycycline, azithromycin and chloramphenicol are effective against this organism.

Infection-associated thrombotic microangiopathy

Acute diarrheal illnesses leading to hypovolemic shock and AKI continue to be common in Asia due to poor sanitation and food hygiene. In a multi-centric cohort study in China, diarrhea and sepsis were the most common causes for CA-AKI in children aged between 1-18 months.⁷⁵ A high suspicion of Shiga toxin producing strains of *E Coli* and *S dysenteriae* infections should be kept if a clinical picture of thrombotic microangiopathy is present. It is being increasingly recognized that thrombotic microangiopathy secondary to pre-existing complement regulation abnormalities can be precipitated by these infections.^{29 28} Direct toxin mediated tissue or cell injury, pathogen associated complement and coagulation activation, and infection associated

acquired antibodies against factor H leading to complement dysregulation are likely mechanisms. The role of underlying abnormalities in complement regulatory genes is being recognized and requires more studies. This recognition is important, as specific treatment like plasmapheresis or anti C5 monoclonal antibody eculizumab might be offered to these patients.^{29,76}

Acute glomerulonephritis

Infection related glomerulonephritis continue to be encountered in Asia secondary to high incidence of infections and large at-risk population. The prototype has been immune complex mediated post streptococcal glomerulonephritis (PSGN). As the childhood infections are better identified and managed, the focus has shifted to adults, in glomerulonephritis develops more commonly alongside staphylococcal infections.⁷⁷ Older adults are relatively more affected, the latent period characteristic of PSGN is missing, and a large proportion do not recover renal function.^{77,78} Diabetes, alcoholism and immunosuppressive state are important associations.^{77,78} A significant proportion of these individuals with para-infectious glomerulonephritis show co-dominant deposition of immunoglobulin A (IgA) in mesangial and/or subepithelial location on kidney biopsy.⁷⁹ The prognosis is poorer than classical IgA nephropathy or PSGN. Recently, the role of inherited or acquired factors leading to complement dysregulation in the causation of infection related glomerulonephritis has been documented.⁸⁰ In a series of 11 patients, functional or genetic abnormalities leading to alternate complement pathway activation were observed in 10.⁸⁰ A close differential is the recently recognized C3 glomerulopathy.^{78 81}

Animal, plant or chemical toxin related AKI

South and South-east Asia continue to have a high burden of snake bite related envenomations and deaths.⁸² Snake bite is an occupational hazard for young active workers in farming and plantations, especially in Cambodia and Vietnam. Called a disease of the poor, its distribution correlates with poor socioeconomic indicators.⁸³ There are significant regional variations in presentation depending on the prevalent species.⁸⁴ AKI is most commonly seen after vasculotoxic snake bite, usually viper. AKI was seen in 18.1% of all snake bite cases that presented to a large academic hospital in North India between 2011-16.⁸⁵ Coagulation abnormalities and oliguria were seen in 88.6% and 79.5% of patients, respectively.⁸⁵ Amongst patients who underwent kidney biopsy, the most common finding was acute tubular necrosis.⁸⁵ WHO suggests a syndromic approach depending of regional epidemiology i.e. narrowing down to type of snake involved based on clinical features and circumstances, and use of anti-venom that covers the most common prevalent snakes that could cause such features in that region.⁸⁴

Human stings by bees, wasps, yellow jackets and hornets are common in Asia, and often complicated by AKI, especially when the victim receives a large dose of venom from multiple stings. In a series of 1091 patients from China, AKI and need of dialysis were seen in 21% and 11% of patients, respectively.⁸⁶ In addition to an early mortality rate of 5.1%, 6% were left with CKD at 6 months.⁸⁶ Similar observations have been noted in other reports from China and Vietnam.^{87,88} Acute tubular necrosis and interstitial nephritis were commonest biopsy findings.⁸⁹ Animal toxin related AKI has also been reported in association with scorpion, spider, giant centipede and jellyfish bites.^{90,91}

The spectrum of AKI following ingestion of plant produce has widened in recent years. Consumption of juice from star fruit (*Averrhoa carambola*), which is rich in oxalate can cause

AKI secondary to acute oxalate nephropathy.^{92,93} Other plants that can cause AKI include certain species of mushroom,⁹⁴ and fruits, flowers and roots from plants like *Gloriosa superba* and *Cleistanthus collinus*.^{95,96} Acute interstitial nephritis and acute tubular necrosis have been described in mushroom poisoning.⁹⁷ Similarly, AKI continues to be encountered in the context of chemical poisonings with copper sulfate, paraquat, aluminium phosphide, chromic acid and melamine in milk formulae.⁹⁸ Awareness of these causes is important, as patients often fail to disclose use of these agents and targeted questioning is required.

Obstetric AKI

Improvements in obstetric care have led to a substantial decline in the prevalence of obstetric AKI in many parts of Asia. Still, third-trimester AKI continues to be encountered, mostly in the settings of pre-eclampsia/eclampsia, HELLP (pre-eclampsia, hemolysis, elevated liver enzymes and thrombocytopenia) syndrome and post-partum hemorrhage.⁹⁹ Although declining, post-abortal and puerperal sepsis leading to AKI continue to be seen in India, Pakistan, Bangladesh and Thailand.^{18,100-103} Recent years have seen the emergence of thrombotic microangiopathies as an important cause of obstetric AKI.¹⁰⁴ Emerging data suggests that many of these are secondary to inherited abnormalities in complement pathway that get unmasked during stresses of pregnancy leading to full clinical expression of the condition.¹⁰⁴ It is important to recognize these cases since they may benefit from plasmapheresis and/or anti-complement therapies.

CA-AKI: HOW TO IMPROVE OUTCOMES?

As evident from the above description, the prevalence, pattern and outcome of CA-AKI are directly related to prevailing public health issues in Asia, and require public health approaches to solve them. An accurate mapping of the disease burden along with detailed documentation

of organ involvement is the first step. This allows generation of data that helps in calculation of costs to provide much-needed care. Prevention is the only recourse to save lives because of the challenges involved in setting up diagnostic and treatment services, including dialysis. The economic consequences of lost productivity, along with the recognition that better and earlier preventive care is a less expensive alternative to treating disease after development should be calculated and presented to policymakers in the form of numbers needed to treat and savings accrued to the health care system.¹⁰⁵ Objectives of prevention programs should be clearly stated and prioritized, based on local resources. Country-specific challenges should be identified and addressed. Some countries have made impressive progress in prevention of diarrhea-related deaths by making effective public health interventions and these lessons should be adopted in other regions as well. AKI and deaths due to diarrheal diseases, which were responsible for 27% of all flood-related mortality in Bangladesh in 1988, have been virtually eliminated, even though the number of individuals who develop diarrhea after floods has actually increased. The interventions include use of water purification tablets, application of bleaching powder and other germicides at flood shelters and aggressive oral rehydration.¹⁰⁶

On the other hand, an example of persisting challenge is management of snake-bites, related to quality control of locally produced antivenom, supply of anti-venom to remote locations, and development of protocols for judicious use in the community. Well-defined diagnostic and treatment protocols for establishing diagnosis in patients with undifferentiated febrile illness will help in early and appropriate management, thereby preventing or accelerating resolution of AKI.

Upcoming challenges should be anticipated and appropriate plans developed to address those. Examples include preparedness for preventing and managing AKI during recurring natural

events like floods and infection outbreaks; training non-physician healthcare workers to identify and mitigate AKI risk, contingency plans in areas prone to natural disasters like earthquakes and tsunamis, and anticipation of long-term consequences of climate change. This needs to be coupled with raising awareness about AKI amongst medical and non-medical caregivers.

Non-modifiable geographical factors like tropical and sub-tropical ecology favoring persistence and growth of microbes, and environmental exposures will continue to pose a risk, suggesting need for continued vigilance, and availability of resources for prevention, timely diagnosis and appropriate treatment.

Most of the research in AKI is concentrated on hospital-acquired AKI, driven by priorities of industrialised developed countries. Nephrology community in developing countries of Asia needs to develop a context-specific research agenda for CA-AKI, which is a more consequential problem for the region. This includes better understanding of disease epidemiology, research in developing appropriate point of care tools to risk-stratify and identify early stages of AKI in the community, evaluating the efficacy and effectiveness of preventive interventions, understanding factors behind drug-resistance in disease causing micro-organisms or vectors and nature of factors that prevent residual improvement in obstetric AKI. Addressing these issues will require a multidisciplinary and cooperative approach with involvement of health systems experts, clinicians, health economists and basic scientists across different Asian countries.

Given the non-availability of resources, the issue of providing dialysis requires addressing. The ISN *Oby25* Snapshot Study showed that 21.3% of all patients who needed dialysis did not

receive this life-saving treatment.⁵ In LLMICs, lack of resources and inability to afford therapy accounted for 46% of such cases.⁵ Promoting the use of peritoneal dialysis that can be done anywhere can be life-saving.¹⁰⁷ The ISN, in partnership with ISPA, IPNA and Sustainable Kidney Care Foundation has been providing acute PD to children with AKI in many parts of the world where there is no dialysis through the Saving Young Lives project.¹⁰⁸

In conclusion, CA-AKI is an important, and growing, public health problem in Asia. Substantial progress has been made over the last decade, but the scope for improvement is still huge. Targeting persisting public health problems, raising awareness and improving healthcare access have the potential to save thousands of lives annually. The success of interventions is critically dependent on understanding the local context and finding tailored local solutions. Emerging knowledge driven by context-specific research agenda offers the opportunity to develop specific strategies to mitigate the burden of CA-AKI and its consequences in Asia.

Table 1: Community and hospital acquired acute kidney injury

	Community acquired	Hospital acquired
Geography	Developing world, especially tropical countries	Developed world and tertiary care hospitals in developing world
Age	Usually younger	Usually elderly
Clinical setting	Tropical infection, volume loss secondary to diarrhea, obstetric accidents, snake bite or insect stings, toxic AKI secondary to consumption of nephrotoxic plants or animal products	Already hospitalized with pre-existing illnesses like complex surgeries, sepsis, organ failure.
First encounter	Communities or clinics	Usually in ICUs
Timing of AKI	At initial presentation or within 48 hours of hospitalization	Develops >48 hours after admission
Manner of identification	Elevated serum creatinine in someone with a known baseline, or demonstration of a decline in creatinine in those with elevated creatinine value at presentation	Progressive rise in creatinine over baseline or new onset reduction in urine output
Pre-existing CKD	Usually absent	Usually present
Organ involved	Kidney often only involved organ, other specific organs involved depending on initiating cause	Multiple organs requiring support
Identification	Presentation in late stages, with complications and imminent need for RRT	Identified on investigations, earlier stages more common
Course of AKI	Usually well-defined, depends on basic illness	Protracted
Long-term outcome	Data poor, recovery likely complete if basic disease recovers. Some forms (e.g. HUS, ACN) may not recover.	Recovery likely partial, high likelihood of progressive CKD despite improvement of precipitating causes

Table 2: Common causes of CA-AKI in Asia

Category	Common causes
Infections	Acute diarrheal illness Malaria Leptospirosis Dengue fever Scrub typhus Typhoid fever Viral hemorrhagic fever Zygomycosis Acute febrile illness: Undifferentiated
Drug induced	Alternative or traditional drugs which are directly nephrotoxic Inappropriate or indiscriminate use of drugs e.g. NSAIDS, aminoglycosides Hemolysis in G-6-P-D deficient individuals
Obstetric AKI	Pre-eclampsia related Ante-partum hemorrhage Post-partum hemorrhage Puerperal sepsis Post-abortal sepsis
Toxic envenomation secondary to animal bite	Snake bite Wasp, bee or hornet stings Spider bite Scorpion sting
Chemical poisoning	Copper sulphate Paraquat Aluminium phosphide
Others	Natural disasters like floods, earthquakes. Dehydration in hot environment Plant toxins e.g. star fruit Mismatched blood transfusions

Table 3: Common differential diagnosis of tropical acute febrile illness associated with CA-AKI in Asia. ¹⁰⁹

Clinical picture	Differential diagnosis
Fever + jaundice	Leptospirosis, malaria, dengue, 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 4: Mechanisms of AKI in tropical infections*
Direct involvement of kidneys by micro-organisms
Tubulo-interstitial injury
Injury to glomerular endothelium
Renal vascular thrombosis
Indirect involvement secondary to systemic effects of infection
Hemolysis
Rhabdomyolysis
Hypovolemic shock
Septic shock
Microvascular injury
Immune complex deposition in glomeruli
Drugs used to treat infections
Hemolysis
Allergic tubulo-interstitial nephritis
Direct nephrotoxicity e.g. aminoglycoside induced acute tubular injury

*Multiple mechanisms may be found in an individual patient.

Table 5: Common morphologic forms of renal injury in AKI related to tropical infections*

Glomerular

Immune complex glomerulonephritis

Thrombotic microangiopathy

Tubulo-interstitial

Acute tubular necrosis

Acute tubulo-interstitial nephritis

Granulomatous interstitial nephritis

Vascular

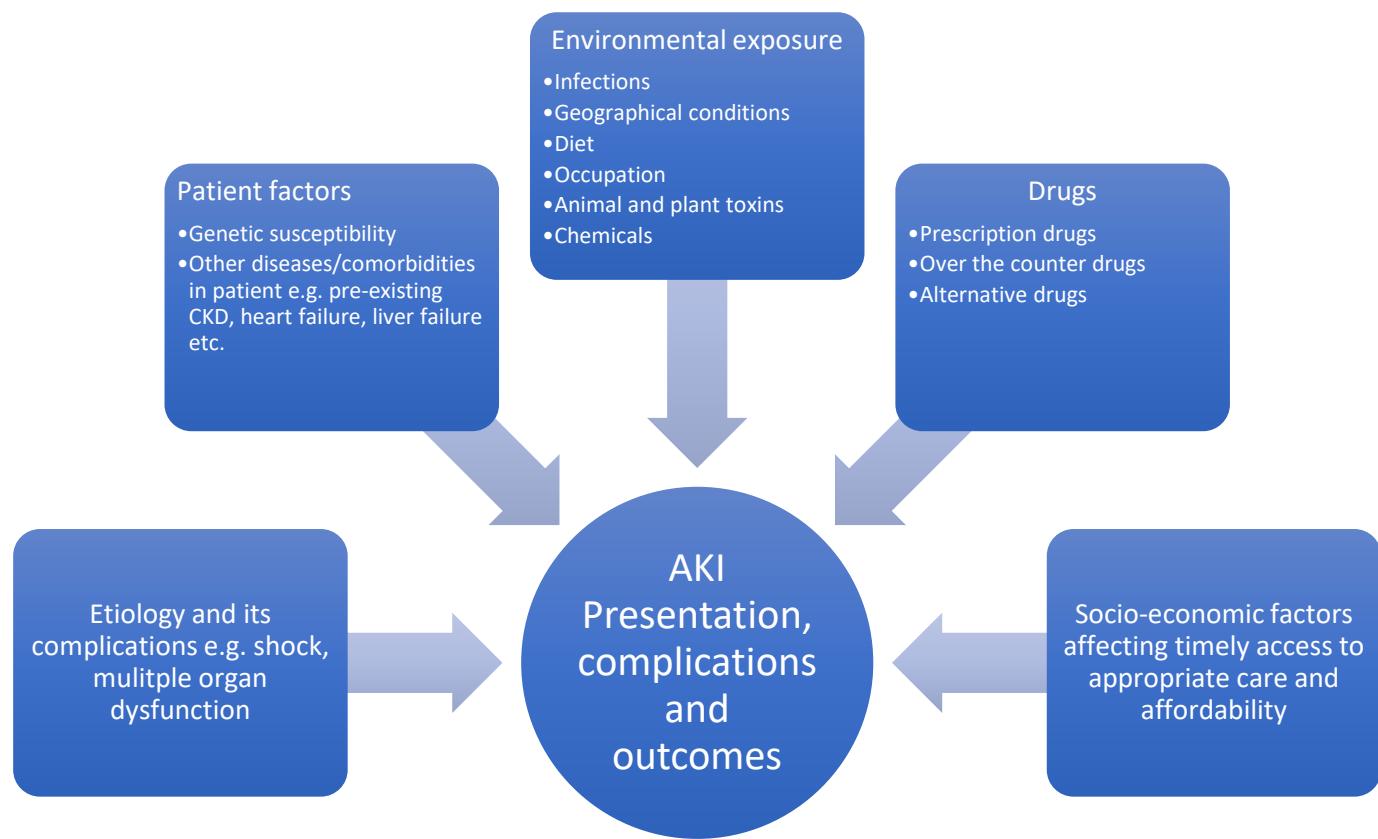
Vascular thrombosis (e.g. acute gastroenteritis in children, angio-invasive mucormycosis)

Thrombotic microangiopathy

Acute cortical necrosis

*These are not mutually exclusive. Mostly a combination of these with one predominant form would be found in an individual patient.

Figure 1: Factors determining presentation, complications and outcomes of AKI



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