The Ongoing Saga of Acute Kidney Injury Associated with Gastroenteritis in Developing World

The incidence of acute kidney injury (AKI) is reported as 22% in the high-income countries (HIC) and 7.5% in lower- and lower-middle-income countries (L/LMIC).[1] AKI in HIC is different from AKI in L/LMIC [Table 1]. Prerenal AKI is the most common cause of AKI in L/LMIC and the predominant cause of prerenal AKI is acute gastroenteritis (GE) [Figure 1].

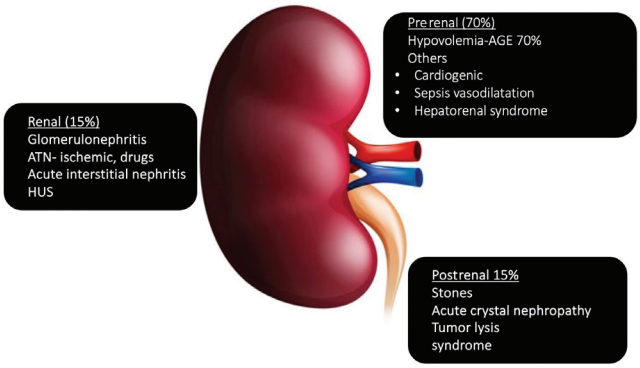

Figure 1: Etiology of AKI. AGE: acute gastroenteritis, ATN: acute tubular necrosis, HUS: hemolytic uremic syndrome, AKI: acute kidney injury

In a study in this issue of IJN, among 923 adults admitted with GE, 10.07% of the patients had AKI.[2] In a study from Saudi Arabia, which included both adults and children, in 300 patients with GE, 41 (13.6%) had AKI.[3] Bradshaw *et al.* showed that one in ten adults hospitalized with acute gastroenteritis (AGE) experienced AKI.[4] GE is a common ailment and 10% incidence of AKI in GE in the current study implies a substantial disease burden.

In the current study, among 313 AKI patients treated in the hospital, 29% was attributed to AGE.[2] In an earlier study done two decades ago, among 187 cases of AKI in a government hospital, 23.5% was attributed to GE.[5] Thus, despite marked improvement in sanitation and several schemes for control of diarrhea, it is unfortunate that GE-AKI remains the predominant cause of AKI. Vairakkani *et al*. reported a lower incidence of GE-AKI which accounted for only 5% of the total AKI burden.[6] This may reflect a seasonal variation with a higher incidence during monsoons. GE-AKI is significantly more common in the elderly.[4,5] However, in the current study, patients above 70 years were excluded.

Those with comorbidities may be more prone to GE-AKI. In a study by Bogari *et al*., the most common comorbidity was malignancy, especially leukemia and lymphoma.[3] Chronic kidney disease (CKD) and hypertension were associated with increased odds of AKI.[4] In the current study, 28% had type 2 diabetes, 30% were hypertensive, and 24% had a history of alcohol consumption. However, patients who had a prior history of CKD, prior renal transplant, or patients having contracted kidneys were excluded; hence the incidence of AKI in the current study might have been lower than studies that included these risk groups.[2]

In the current study,[2] 8.6% of GE was attributed to *Vibrio cholerae*, while cultures were negative in others due to prior antibiotic use. Viral studies were not done in the current study. In a study by Tatte *et al*., in 110 adults with AGE from Western India, the prevalence of enteric viruses was rotavirus A (RVA): 38.5%; enterovirus, 23.1%; astrovirus, 23.1%; adenovirus, 7.7%; human bocavirus, 7.7%; and norovirus, 0%.[7] The nonviral causes include bacteria (e.g., *Staphylococcus aureus*, *Campylobacterjejuni*, *Shigella* spp, *Salmonella* spp, *Yersinia*, and *Escherichia coli*) and parasites (e.g., *Giardia* and *Cryptosporidium*). In a study from Saudi Arabia, the most frequent cause of AGE was *Salmonella spp*. (n = 163, 53.3%) and AKI was seen in 36.5% with Salmonella infection while *Clostridium difficile* diarrhea was associated with AKI in 51.2%.[3] Norovirus, often reported as a frequent cause of AGE was not documented in these studies.

The major pathogenetic mechanism of AKI in AGE is prerenal or ATN. However, severe ATN may activate toll-like and other pattern recognition receptors on resident immune cells with microinflammation with infiltration of

Table 1: AKI in HIC versus L/LMIC

	HIC	L/LMIC
Type	Hospital setting	Community acquired
Age	Older	Younger
Comorbidities	Diabetic, multiple comorbidities, CKD, cardiovascular disease	Usually none, occurs in healthy individual
Etiology	Nephrotoxins, contrast, cardiogenic	Gastroenteritis, infections, toxins, insect bites
Prognosis	Poor	Better
Prevention	Difficult as multiple comorbidities	Preventable

HIC: high-income countries, L/LMIC: lower-middle-income countries, AKI: acute kidney injury, CKD: chronic kidney disease

neutrophils, M1 macrophages, generation of cytokines, oxidative stress, and endothelial dysfunction. Unless there is prolonged hypoperfusion, numerous counter-regulators promote resolution of necroinflammation and healing. Regeneration occurs by the proliferation of progenitor cells (immature tubular cells) which exist along the nephron. If these cells are lost, as occurs in severe ATN/cortical necrosis, there is permanent loss of renal tissue.

Renal biopsy is indicated only in cases where recovery is delayed for more than two weeks or urine shows RBC and/or protein. Histology commonly shows acute tubular injury. In this study, ATN, and less commonly acute tubulointerstitial nephritis, were the commonest findings. Other lesions like hemolytic uremic syndrome, acute cortical necrosis, and proliferative glomerulonephritis may be seen rarely.[2]

AKI is mostly prerenal and can be prevented if identified early. Bogari *et al*. showed that 96.4% patients with AKI had mild dehydration.[3] Thus, kidney injury can be induced even by mild dehydration. Mahajan *et al*. noted that volume depletion was the most common precipitating factor for AKI.[8] Rapid and effective restoration of extracellular fluid (ECF) volume within 4 h can prevent AKI.[9] A significant proportion of patients with GE in the current study presented with shock, which highlights the lack of awareness of the public about early fluid resuscitation and also the inadequate implementation of standard protocols for volume resuscitation at the primary care level.

In the current study,[2] 71% were classified as having KDIGO stage 3 AKI, vasopressor support was required in 22.6% due to refractory hypotension, and 29% required dialysis, while in another study,[5] 64.1% needed dialysis. The dialysis rates may be higher in a tertiary hospital or those with a policy of early initiation of dialysis. Low rates of dialysis requirement in the current study may be due to early referral to the nephrology unit. Both peritoneal dialysis (PD) and hemodialysis (HD) are effective. In Muthusethupati's study, 71.6% were managed by PD alone.[6] PD is also more frequently used in LMIC: in children, those with shock, and when patients cannot be shifted to dialysis units. CRRT can also be offered; however, cost is prohibitive.

In the current study, 84.9% had complete recovery while 8.6% of patients progressed to CKD.[4] In another study, CKD occurred in 24.6% of a general hospitalized population with varying causes of AKI after three years of follow-up.[10] Thus, it is imperative to manage GE-AKI effectively to prevent progression to CKD. Though most cases in the current study recovered, this does not necessarily represent regeneration of the affected tubular cells, as some tubular cells die and do not regenerate but GFR still returns to normal by compensatory hypertrophy of unaffected tubular epithelial cells. This is a risk factor for CKD.

In the 1990s, the mortality was high—28% in one study[5] and 53.7% in another.[11] The current study reported 6.5% mortality which may reflect better awareness about AKI and availability of dialysis. Though predictors of mortality could not be assessed in this study, metabolic acidosis, hypotension, encephalopathy sepsis, advanced AKI stage, mechanical ventilation, leukocytosis, and hyperkalemia were associated with in-hospital mortality in most studies. Though the mortality was lower in this study as compared to the previous studies, it still does not meet the KDIGO goal of "0" preventable deaths from AKI.

This important study highlights that while we focus on novel and emerging causes of AKI, we often tend to neglect GE-AKI, which accounts for almost 30% of all cases of AKI. Majority of patients present late with shock—fluid resuscitation is often late and inadequate. Unlike other causes of AKI, GE-AKI is largely preventable with the provision of safe drinking water, provision of toilet facilities, education about handwashing and oral rehydration therapy at the public health level, and implementation of SOPs for volume resuscitation at the level of primary care centers and in ICUs. Prevention of GE-AKI will be a huge step toward realizing the International Society of Nephrology (ISN) goal of "0 by 25" and will also help reduce the CKD burden.

Conflicts of interest

There are no conflicts of interest.

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Mind the Gap in Kidney Care: Translating What We Know into What We Do

Historically, it takes an average of 17 years to move new treatments from clinical evidence to daily practice. Given the highly effective treatments now available to prevent or delay kidney disease onset and progression, this is far too long. The time is now to narrow the gap between what we know and what we do. Clear guidelines exist for the prevention and management of common risk factors for kidney disease, such as hypertension and diabetes, but only a fraction of people with these conditions worldwide are diagnosed, and even fewer are treated to target. Similarly, the vast majority of people living with kidney disease are unaware of their condition, because in the early stages it is often silent. Even among patients who have been diagnosed, many do not receive appropriate treatment for kidney disease. Considering the serious consequences of kidney disease progression, kidney failure, or death, treatments must be initiated early and appropriately. Opportunities to diagnose and treat kidney disease early must be maximized beginning at the primary care level. Many systematic barriers exist, ranging from patient to clinician to health systems to societal factors. To preserve and improve kidney health for everyone everywhere, each of these barriers must be acknowledged so that sustainable solutions are developed and implemented without further delay.

At least one in ten people worldwide is living with kidney disease.[1] According to the Global Burden of Disease study, in 2019, >3.1 million deaths were attributed to kidney dysfunction, making it the seventh leading risk factor for death worldwide [Figure 1 and Supplementary Figure S1].[2] However, global mortality from all kidney diseases may actually range between 5 and 11 million per year, if the estimated lives lost, especially in lower-resource settings, from acute kidney injury and lack of access to kidney replacement therapy for kidney failure (KF) are also counted.[3] These high global death rates reflect disparities in prevention, early detection, diagnosis, and treatment of chronic kidney disease (CKD).[4] Death rates from CKD are especially prominent in some regions, and particularly high in Central Latin America and Oceania (islands of the South Pacific Ocean), indicating the need for urgent action.[5]

CKD also poses a significant global economic burden, with costs increasing exponentially as CKD progresses, not only because of the costs of dialysis and transplantation, but also because of the multiple comorbidities and complications that accumulate over time.[6,7] In the United States, Medicare fee-for-service spending for all beneficiaries with CKD was $86.1 billion in 2021 (22.6% of the total expenditure).[8] Data from many lower-resource settings are absent, where most costs are paid for out of pocket. A recent study from Vietnam reported that the cost of CKD per patient was higher than the gross domestic product per capita.[7] In Australia, it has been estimated that early diagnosis and prevention of CKD could save the health system $10.2 billion over 20 years.[9]

Although there is regional variation in the causes of CKD, the risk factors with the highest population-attributable factors for age-standardized CKD-related disease-adjusted life years were as follows: high blood pressure (51.4%), high fasting plasma glucose level (30.9%), and high body mass index (26.5%).[10] These risk factors are also global leading risk factors for death [Figure 1]. Only 40% and 60% of those with hypertension and diabetes, respectively, are aware of their diagnosis, and far smaller proportions are receiving treatment and at target goals.[11,12] Moreover, at least one in five people with hypertension and one in three people with diabetes also have CKD.[13]

A large proportion of CKD can be prevented through healthy lifestyles, prevention and control of risk factors, avoidance of acute kidney injury, optimization of maternal and child health, mitigation of climate change, and addressing social and structural determinants of health.[3] Nevertheless, the benefits of some of these measures may only be seen in generations to come. In the meantime, early diagnosis and risk stratification create opportunities to institute therapies to slow, halt, or even reverse CKD.[14]