Acute Kidney Injury in Western Countries

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Key Words

Acute kidney injury · Epidemiology · Mortality · Outcomes · Renal replacement therapy

Abstract

Background: Acute kidney injury (AKI) is frequent and is associated with poor outcomes, including increased mortality, higher risk of chronic kidney disease, and prolonged hospital lengths of stay. The epidemiology of AKI mainly derives from studies performed in Western high-income countries. More limited data are available from Western low-income and middle-income countries (LMICs) located in Central and South America. **Summary:** In this review, we summarize the most recent data on the epidemiology of AKI in Western countries, aiming to contrast results from industrialized high-income countries with LMICs. The global picture of AKI in LMICs is not as well characterized as in the USA and Europe. In addition, in some LMICs, the epidemiology of AKI may vary depending on the region and socioeconomic status, which contributes to the difficulty of getting a better portrait of the clinical condition. In low-income regions and tropical countries, AKI is frequently attributed to diarrhea, infections, nephrotoxins, as well as obstetric complications. As opposed to the situation in high-income countries, access to basic care in LMICs is limited by economic constraints, and treatment is often delayed due to late presentation and recognition of the condition, which contribute to worse outcomes. In addition, dialysis is often not available or must be

paid by patients, which further restricts its use. **Key Messages:** There are great disparities in the epidemiology of AKI between Western high-income countries and Western LMICs. In LMICs, education and training programs should increase the public awareness of AKI and improve preventive and basic treatments to improve AKI outcomes. **Facts from East and West:** (1) More than 90% of the patients recruited in AKI studies using KDIGO-equivalent criteria originate from North America, Europe, or Oceania, although these regions represent less than a fifth of the global population. However, the pooled incidence of AKI in hospitalized patients reaches 20% globally with moderate variance between regions. (2) The lower incidence rates observed in Asian countries (except Japan) may be due to a poorer recognition rate, for instance because of less systematically performed serum creatinine tests. (3) AKI patients in South and Southeastern Asia are younger than in East Asia and Western countries and present with fewer comorbidities. (4) Asian countries (and to a certain extent Latin America) face specific challenges that lead to AKI: nephrotoxicity of traditional herbal and less strictly regulated nonprescription medicines, environmental toxins (snake, bee, and wasp venoms), and tropical infectious diseases (malaria and leptospirosis). A higher incidence and less efficient management of natural disasters (particularly earthquakes) are also causes of AKI that Western countries are less

For acute kidney injury in Asia, see Yang, Kidney Dis 2016;2:95–102.

likely to encounter. (5) The incidence of obstetric AKI decreased globally together with an improvement in socioeconomic levels particularly in China and India in the last decades. However, antenatal care and abortion management must be improved to reduce AKI in women, particularly in rural areas. (6) Earlier nephrology referral and better access to peritoneal dialysis should improve the outcome of AKI patients.

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Introduction

Acute kidney injury (AKI) is frequent, occurring in 21% of hospital admissions worldwide [1], and is associated with increased morbidity, mortality, and cost [2, 3]. The epidemiology of AKI mainly derives from studies performed in Western high-income countries [1, 4], as low-income and middle-income countries (LMICs) do not necessarily have the infrastructure to collect and report their data.

A worldwide meta-analysis published in 2013 using KDIGO-equivalent criteria for AKI diagnosis [4, 5] has shown that out of 147 AKI studies performed between 2004 and 2012, 41% originated from Europe and 43% from North America [4]. Very limited data are available from LMICs located in South and Central America [1]. In these regions, only 3% originated from South America and none from Central America [1, 4]. Moreover, almost all studies from South America were performed in critically ill patients in Brazil, further limiting comparisons between countries [1, 4]. Most other reports from LMICs were performed in a single center and described AKI due to a single disease without reference to the underlying population [1]. Data on community-acquired AKI in rural areas are therefore missing [1]. In addition, the size of the studies varied widely between regions. Although 85% of the world population resides in LMICs, studies from North America included a total of 1,843,243 patients, those from Europe 917,492 patients, and those from South America 3,046 patients only [4].

As opposed to previous results, the most recent meta-analysis on worldwide AKI showed that the pooled incidence in LMICs around the world is now close to that of developed countries [1]. This may be due to an increased awareness of AKI, increased diagnostic capacities and accessibility of services, and the use of comparable definitions (KDIGO or KDIGO-equivalent) [1]. However, there are still gaps in the knowledge about the factors affecting AKI incidence and outcomes worldwide. Varia-

tions in climate, ethnicity, culture, and socioeconomic status affect the etiology and management of AKI, which contributes to influence mortality and nonrecovery of renal function. However, these variations and their effect on outcomes have not been properly quantified. The current review focuses on the epidemiology, etiology and patterns, recognition and management, as well as outcomes of AKI in Western countries (table 1).

Epidemiology of AKI in Western Countries

In recent meta-analyses [1, 4], the pooled incidence of AKI in hospitalized patients using a KDIGO-equivalent AKI definition was 22.3% in North America, 31.0% in South America, and 16.9% in Australia and New Zealand, and varied between 19.3 and 25.2% in Europe [1]. As seen in Asia, most of the publications still came from large academic hospitals and included critically ill and/or septic patients, or those who underwent cardiac surgery or who received nephrotoxins. Consequently, the AKI incidence in community hospitals and rural areas is unknown [1, 4].

The incidence of AKI is increasing [6–8] and may double over the next decade [9, 10]. AKI is increasing mainly in patients with acute illness and possibly in those undergoing major surgery, which may be related to improved ascertainment in administrative databases and higher sensitivity of diagnostic criteria, older populations with additional comorbidities and the occurrence of more frequent modifiable risk factors, such as sepsis, administration of iodinated contrast, and exposure to nephrotoxins [8]. In a recent multivariate logistic regression to identify diagnoses and procedures that may affect the increased risk of dialysis-requiring AKI in the USA, diagnoses such as sepsis, hypertension, respiratory failure, hemorrhagic disorders, shock, and liver disease were associated with more frequent dialyses but not surgeries or other procedures [11].

Community-Acquired AKI and Hospital-Acquired AKI (General Hospital Wards)

There are very limited reports on community-acquired AKI [6, 12]. The worldwide meta-analysis on AKI previously mentioned has shown that only 7 (5%) of 147 studies focused on community-acquired AKI [4]. According to these studies, the overall incidence of AKI was 8.3% [4]. One study has quantified the incidence of non-dialysis-requiring and dialysis-requiring AKI among members of a large integrated health-care delivery system in California [6]. Between 1996 and 2003, the incidence

Table 1. Differences in the epidemiology and outcomes of AKI between high- and low-income Western countries

	High income	Low income
Incidence	Increasing	Increasing
Etiologies	Sepsis, hypovolemia, drugs, and ischemia	Similar etiologies in urban areas; more diarrhea, tropical diseases, animal venoms, and obstetric complications in rural areas
Types of population	Often older patients with multiple comorbidities	Similar populations in urban areas; younger populations in rural areas
Location	Often in intensive care units	More often community acquired
Number of organs affected	Often associated with multiorgan failure	More often a single-organ disease in rural areas
Availability of dialysis	Not a concern to most patients	Major issue
Mortality	Overall decreasing; higher mortality if associated with multiorgan failure	Overall decreasing; mortality seems higher than in high-income countries for similar disease severity
Cost	Very high	Depending on resources
Prevention	Avoidance of nephrotoxins, more difficult to prevent	Importance of timely hydration and treatment of infections
Report	Excellent data	Limited data

Adapted from Mehta et al. [1].

of non-dialysis-requiring AKI increased from 322.7 to 522.4 per 100,000 person-years and that of dialysis-requiring AKI from 19.5 to 29.5 per 100,000 person-years [6]. In another European study performed 20 years ago, the overall incidence of AKI was 209 cases per million population, and AKI occurred in 52% of patients at hospital admission and later on during the hospital stay in the remaining patients (48%) [12].

Hospital-acquired AKI outside intensive care units is also not well described. In the meta-analysis, 50 (34%) AKI studies were either hospital acquired or unspecified [4], and the AKI incidence was 20.7% [4]. No further characterization was available. A recent large study in 10 hospitals in England and Scotland identified AKI in 18% of patients, which is consistent with results from the worldwide meta-analysis [13]. In LMICs, insufficient monitoring of serum creatinine in hospitalized patients may also miss a significant proportion of patients with the condition.

Intensive Care Unit

AKI is well described in critically ill patients. As reported in one of the two worldwide meta-analyses, 24% of studies were performed in critically ill patients, 29% in cardiac surgery patients, and 3% in patients who experienced trauma [4]. Therefore, 56% of all AKI studies included patients at least transiting in the intensive care unit. The worldwide pooled AKI incidence in critically ill patients was 30.9% [4]. In comparison, 24.3% of patients undergoing cardiac surgery or 19.9% of trauma patients had AKI. However, there are large variations in the incidence and severity of AKI in similar settings. For example, studies have shown AKI rates between 12 and 45% following cardiac surgery [14, 15]. These differences may be related to variations in comorbidities and practice patterns.

Causes and Patterns of AKI in Western Countries

AKI can be caused by multiple different insults, and patterns of AKI are different across the world [1]. In high-income countries, patients are older and have more comorbidities, such as diabetes mellitus, cardiovascular disease, malignancy, and possibly chronic kidney disease (CKD) [1, 16]. The most common causes for AKI in high-income countries are sepsis, hypovolemia, drugs, and ischemia [1, 16, 17], and AKI is often associated with other acute organ failures [16, 17].

AKI caused by sepsis, hypovolemia, drugs, and ischemia also occurs in LMICs, mainly in urban areas. Other causes of AKI, such as glomerulonephritis and acute interstitial nephritis, are more often diagnosed in intensive care units in LMICs than in high-income countries [16]. However, it is unclear whether these represent real differences or whether they reflect variations in practice patterns regarding kidney biopsies. In one multicenter international study on AKI in critically ill patients, no kidney biopsy was done in developed countries, while 5.2% of patients from emerging countries had a biopsy performed [16].

In LMICs, the etiologies of AKI vary depending on the region [1]. In tertiary hospitals in urban areas, causes are similar as in high-income countries [18] but may also include tropical infectious diseases such as malaria, leptospirosis, and dengue [19, 20]. In rural areas, AKI is often attributed to diarrhea, tropical infectious diseases, animal venoms, natural medicines and dyes, and obstetric complications including septic abortion [1, 21, 22]. Unfortunately, these conditions often affect younger people without comorbidities.

Tropical Infectious Diseases Causing AKI

Malaria is a common cause of AKI in tropic communities mainly attributed to *Plasmodium falciparum* and less often to *Plasmodium vivax* infection. Reports on AKI and malaria from Western countries are very limited, but the incidence is increasing in Africa and Asia [2]. Following *P. falciparum* infection, AKI will occur in 1–4% of patients but may occur in up to 60% depending on the region [2]. Risk factors for AKI are not well characterized [23, 24]. Prompt initiation of antimalarial drugs, surveillance of kidney function, and initiation of dialysis if required can contribute to improve survival and facilitate renal recovery [23].

Leptospirosis, a spirochetal zoonosis, is often misdiagnosed as another disease such as dengue in South America despite its resurgence [25]. In urban Brazil, outbreaks of leptospirosis often follow heavy rain and flooding, as humans get infected either by exposure to contaminated water from infected animal urine or occupational contact with infected animal tissue. Up to 80% of infected patients will develop AKI [26], and dialysis has been required in 38% of adults suffering from the infection in a Brazilian cohort [26]. Early administration of antibiotics may reduce the likelihood of progression to severe disease for some patients [27].

Dengue is a frequent viral infection transmitted by a mosquito bite that represents a major threat to public health worldwide according to experts in the field [28]. AKI is a serious complication of dengue, and its frequency is not well characterized but seems to occur in 1–13% of patients [28]. In a retrospective study from a tertiary infectious diseases hospital in Brazil, 4% of critically ill patients with AKI were affected by dengue [20]. Human immunodeficiency virus (30%), tuberculosis (12%), and leptospirosis (11%) occurred more frequently than dengue [20]. Treatment for dengue is mainly supportive, and although rhabdomyolysis is rarely associated with dengue, monitoring of serum creatine kinase levels is required to promptly diagnose and treat this condition which can further contribute to AKI. The pathophysiology of rhabdomyolysis in dengue may be caused by direct viral invasion or be mediated by myotoxic cytokines, such as tumor necrosis factor [28].

Environmental Nephrotoxin-Induced AKI

In a tertiary care center in Brazil, out of 276 victims of snakebites, AKI was observed in 15% [29]. These patients were young (43 ± 20 years). A longer time having elapsed between the snakebite and medical care and between the snakebite and antivenom was associated with AKI. Dialy-

sis was required in 30% of patients, and renal recovery was present in 55% of patients at discharge.

AKI in Pregnancy

AKI in pregnancy (P-AKI) is a cause of significant fetomaternal mortality and morbidity, mainly in developing countries [30]. Hypertensive disorders of pregnancy [preeclampsia/eclampsia or hemolysis, elevated liver enzymes, and low platelet count syndrome (HELLP)] are the leading causes of P-AKI worldwide [30]. The incidence of P-AKI has declined in developed countries over the last three decades due to the decreased incidence in septic abortions and a better management of hypertensive disorders of pregnancy [30]. However, a recent large Canadian study has shown that rates of obstetric AKI increased from 1.7 to 2.7 per 10,000 deliveries between 2004 and 2010 (61% increase, 95% CI 24–110) [31]. The increase was related to hypertensive disorders, especially gestational hypertension with significant proteinuria (adjusted increase 171%, 95% CI 71–329%). In developing countries, the incidence of P-AKI remains high but seems to decrease [30] and is more often attributed to septic abortions, poor follow-up of pregnancy with limited screening, and late referral of hypertensive complications of pregnancy [30]. Significant mortality is associated with P-AKI. As shown in a series of 55 patients from a Brazilian hospital, maternal mortality was 31% [32].

Recognition and Management of AKI in Western Countries

Recognition

Even in developed countries where resources are easily available for AKI diagnosis, the recognition of AKI can be problematic. A recent assessment of the quality of care in the UK found that AKI was not recognized in 24% of 1,577 patients [33]. Moreover, advisers from the UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD) study found that 43% of patients had an improper delay in the diagnosis of posthospitalization AKI [34].

There are controversial data on the effect of electronic alert protocols to detect AKI and improve outcomes. Korean investigators reported on an electronic AKI alert protocol warning physicians and recommending prophylactic measures to prevent contrast-induced AKI when an investigation using contrast was ordered for patients with an estimated glomerular filtration rate of 60 ml/min/1.73 m² [35]. This observational study included

463 patients, and the measure increased the use of prophylaxis from 25 to 55% ($p < 0.001$) and lowered the incidence of contrast-induced AKI (10 to 3%, $p = 0.02$) [35]. In a prospective observational study from Belgium including 951 critically ill patients, an electronic AKI alert protocol reduced the time to therapeutic intervention and may have helped to normalize kidney function within hours after an AKI alert ($p = 0.05$) [36]. However, in a single-blinded randomized-controlled trial from the USA including 2,392 hospitalized patients, maximum changes in creatinine, dialysis, and death at 7 days did not differ between alert and usual care groups ($p = 0.88$) [37]. Reasons explaining these discrepant results are not fully understood. It is possible that AKI alerts in critically ill patients were more frequently associated with changes in therapeutic interventions than in hospitalized patients taken care of by physicians not necessarily used to managing AKI. Additionally, the methods of AKI detection and the methods by which results are communicated need to be delineated, as these influence effectiveness [38]. Finally, in developing countries, a significant proportion of hospitalized patients may not have sufficient serum creatinine testing to assess AKI, as shown in Asia.

Management

AKI is often preventable and treatable with timely interventions such as volume repletion and treatment of associated infections [8]. However, the management of AKI is highly variable even in countries with available and accessible resources. Guidelines for AKI management are not universally available or applied [39–41]. In LMICs, the paucity of infrastructure and resources to treat AKI and its complications represent major issues.

In 2013, the International Society of Nephrology instituted the 0by25 initiative [1], aiming to prevent any death from untreated AKI in low-resource regions by 2025. This statement was based on the premise that ‘the ability to provide lifesaving treatments for AKI provides a compelling argument to consider therapy for AKI as much of a basic right as it is to give antiretroviral drugs to treat human immunodeficiency virus in low-resource regions, especially because care needs only be given for a short period of time in most patients’.

Renal Replacement Therapy

The overall proportion of patients with AKI who needed dialysis in KDIGO-defined studies is 11% [1]. It has been estimated that 5% of critically ill patients will require dialysis [42]. If dialysis is unavailable as for most people in LMICs, death ensues because of fluid overload, hyper-

kalemia, and uremic toxins accumulation. In LMICs, there are often no dialysis facilities or no health insurance, so that patients cannot afford dialysis or can only pay for a short period until their financial resources are exhausted [1]. Dialysis availability can vary widely even between different areas of the same country. The use of peritoneal dialysis may facilitate access to dialysis in some parts of the world. Several studies mainly from Brazil have shown that peritoneal dialysis can provide similar outcomes to other dialysis modalities in AKI [43–45].

Renal Referral

Delayed or absent nephrology referral is associated with a higher mortality, dialysis dependence, and length of hospital stay [46–48]. However, given the incidence of AKI, there is an insufficient number of nephrologists to care for all these patients. Therefore, it is essential to properly train primary care physicians to raise AKI awareness, enable prompt identification of patients with AKI, and provide practical management of AKI including nephrology referral if required, especially in LMICs.

Follow-Up

In an ideal world, all patients who survive episodes of AKI should have their kidney function monitored for at least 3 months and possibly longer after hospital discharge. A recent observational study also showed that nephrology follow-up within 90 days of discharge was associated with a lower mortality [49]. However, most patients do not have long-term follow-up of kidney function, and many never see a nephrologist, even in developed countries with universal coverage by national health systems [49]. This may also affect long-term deterioration of renal function and progression to CKD.

Outcomes

The course of AKI varies with its setting, and the severity and duration of AKI affect dialysis requirement, recovery of renal function, and survival. However, it is unclear how exactly variations in processes of care influence outcomes.

Mortality

AKI has been independently associated with an increased risk of adverse outcomes, including death [50]. In the most recent meta-analysis, the overall AKI mortality was just 21%, probably due to the predominance of AKI stage 1 [1]. Indeed, the mortality rates increase with AKI

severity, from 15.9% in stage 1 to 47.8% in stage 3 [4] and 49.3% in dialysis-requiring AKI [4]. Mortality is also higher in emerging compared to developed countries, possibly because of more severe AKI due to late presentation at care facilities or inadequate care [1]. In South America, the pooled mortality was 33.4%, while it was 16.6% in North America and ranged from 17.2 to 26.1% in Europe [4].

Encouragingly, mortality rates attributed to AKI have decreased, at least in high-income countries [4, 7, 51]. In dialysis-requiring AKI, one large study has shown that the 90-day mortality declined from 50% in 1996–2000 to 45% 10 years later [7]. Another study found that in-hospital mortality declined from 41.3 to 28.1% between 1988 and 2002 in patients requiring dialysis, and from 40.4 to 20.3% in all AKI patients [51]. This decrease in mortality may be related to more frequent testing of serum creatinine, increased use of preventive strategies, and avoidance of nephrotoxins including starches [52–54], as well as better patient management, such as earlier initiation of dialysis and avoidance of fluid accumulation [55].

Kidney Outcomes

AKI also affects long-term kidney function, as shown in large studies from the USA and Europe. Since follow-up care is less frequent and longitudinal databases are rare in LMICs, the epidemiology of CKD after AKI is unknown in these countries. For patients who survive hospitalization with acute dialysis, data from high-income countries showed that 5–20% will remain on dialysis at hospital discharge [56]. For patients who recover from AKI within 10 days, the risk of developing stage 3 CKD increases 2-fold by 1 year [57]. In addition, the risk of CKD increases with the number of AKI episodes [58]. It has been estimated that following AKI, the risk of developing CKD increases 8- to 9-fold and for end-stage renal disease 3-fold over the following years [59–62]. CKD and end-stage renal disease both contribute to a poor quality of life and disability in affected patients [60, 63].

Costs

AKI has been independently associated with prolonged hospital lengths of stay [50]. AKI is associated with an up to doubling of hospital costs, independent of other factors [64, 65]. In the USA, a conservative estimate of health-care costs attributed to AKI exceeded USD 10 billion per year 10 years ago [50]. A recent English study showed that the estimated annual cost of AKI care was more than USD 1.7 billion [66]. The use of different dialysis modalities can affect AKI-associated costs. Perito-

neal dialysis is the less expensive option. The use of intermittent hemodialysis or sustained low-efficiency daily dialysis rather than continuous renal replacement therapy could also reduce costs [67–69]. However, if continuous renal replacement therapy improves renal recovery among survivors, it may be worth additional expenses [67]. However, the effect of dialysis modalities on renal recovery is still uncertain.

Future Perspectives

There are great disparities in the epidemiology, recognition, management, and outcomes of AKI between Western high-income countries and Western LMICs. Limited data exist on the incidence and outcomes of AKI in community hospitals and rural areas, even in high-income countries. Worldwide, the incidence of AKI is increasing, but AKI-associated mortality is declining. In high-income countries, education programs should focus on preventing exposure to nephrotoxins, if feasible, and provide adequate management in a timely manner. In LMICs and high-income countries, education and training programs should increase the public awareness of AKI, as highlighted by the Oby25 initiative [1]. Also, education should focus on improving preventive and basic treatments to ameliorate AKI outcomes. Specifically, education programs should focus on the identification of high-risk patients, exposures causing AKI, tests to diagnose AKI, interventions to correct reversible factors, recognition of the need for dialysis, and referral to a nephrologist if needed. These programs need to be tailored to the peculiarities of the different countries and areas, considering health-care resources, personnel, and infrastructure to efficiently improve AKI outcomes.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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