Global Kidney Disease 2

Acute kidney injury: an increasing global concern

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This is the second in a Series of six papers about global kidney disease

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Despite an increasing incidence of acute kidney injury in both high-income and low-income countries and growing insight into the causes and mechanisms of disease, few preventive and therapeutic options exist. Even small acute changes in kidney function can result in short-term and long-term complications, including chronic kidney disease, end-stage renal disease, and death. Presence of more than one comorbidity results in high severity of illness scores in all medical settings. Development or progression of chronic kidney disease after one or more episode of acute kidney injury could have striking socioeconomic and public health outcomes for all countries. Concerted international action encompassing many medical disciplines is needed to aid early recognition and management of acute kidney injury.

Introduction

Until recently, an absence of consensus meant that several different definitions of acute renal failure were in standard use, and wide variation existed in estimates of disease prevalence (1–25%) and mortality (15–60%).[1,2] To resolve this confusion, several definitions and classification systems of acute renal failure have been proposed.[3] All systems were based on reports that even small absolute increases in serum creatinine are linked to poor short-term and long-term prognosis.[4,5] In parallel, the change of the term acute renal failure to acute kidney injury, which encompasses the entire spectrum of disease from small changes in function to requirement for renal replacement therapy (RRT), created a new descriptive system and extended the number of potentially affected patients.

The most recent definition of acute kidney injury retains the Acute Kidney Injury Network (AKIN) and Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) staging criteria, and is proposed by the Kidney Diseases: Improving Global Outcomes (KDIGO) clinical practice guidelines workgroup.[6] The KDIGO criteria stage patients according to changes in serum creatinine and urine output, rather than changes in glomerular filtration rates, apart from in children younger than 18 years (for whom an acute decrease in estimated glomerular filtration rate to less than 35 mL/min per 1·73 m² is included in the stage 3 criteria). Both serum creatinine and urine output criteria are important predictors and the use of RIFLE without assessment of urine output underestimates the incidence and grade of acute kidney injury and can delay diagnosis.[7]

In this Series, we review the increasing incidence of acute kidney injury and complexity behind prevention and management, focusing on differences between high-income and low-income countries.

Key messages

- Incidence of acute kidney injury is steadily increasing in low-income and high-income countries; however, the distribution of causes differs dependent on the location
- Presence of more than one comorbidity results in high severity of illness scores in every medical setting of acute kidney injury
- Pre-existing chronic kidney disease is a potent risk factor for acute kidney injury
- Development or progression of chronic kidney disease after one or more episode of acute kidney injury has substantial socioeconomic and public health effects in high-income and low-income countries

Epidemiology

High-income countries

Incidence of acute kidney injury steadily increased between 1988 and 2003.[8–10] Disease reporting in administrative databases suggests a prevalence of about 2% of patients in hospitals in the USA.[9,10] However, incidence of acute kidney injury in patients with acute myocardial infarction declined between 2000 and 2008, despite a rising prevalence of risk factors, and probably because of an increased awareness of the disease and increasingly effective prevention.[11] Variety in incidence is determined by differences in clinical settings (eg, community,

Search strategy and selection criteria

We searched PubMed and Embase for articles published between Jan 1, 2000, and Jan 31, 2013 without language restrictions with the search terms "AKI" and "acute kidney injury" as the first set of search terms with "epidemiology", "causes", "risk factors", "clinical approach", "prevention and management", "prognosis", and "costs". We primarily included publications from the previous 5 years and articles that assessed developing countries, global health issues, and socioeconomic aspects of acute kidney injury. We added articles not retrieved by the search that were regarded as highly relevant by the authors to the reference list.

hospital, or intensive-care unit) but also emphasises a limitation of some studies and shows that true incidence is not known.

Community-acquired acute kidney injury might have only one cause, whereas the disease can result from several pathways in patients in hospital, especially for those who are severely ill. Risk of death shows a stepwise increase according to the stage of disease.[12] Many patients die from underlying comorbidities and the previously accepted pattern of almost complete recovery of kidney function in survivors of acute kidney injury has been replaced by the notion that partial recovery or non-recovery can occur, especially in patients with pre-existing chronic kidney disease.

The scope of diseases leading to paediatric acute kidney injury has changed. Whereas intrinsic renal disease was the most common cause in the past, acute kidney injury now often accompanies system or extrarenal illness (eg, sepsis, cardiovascular surgery, or organ transplantation) and can be part of a multiorgan failure syndrome.[13]

Low-income countries

Cause and presentation of acute kidney injury in low-income countries differ from that in high-income countries. True epidemiology is not well understood because of late presentation of patients to tertiary centres, under-reporting, and a reduced capacity to provide intensive care to severely ill patients.[14] Problems related to acute kidney injury lead to up to 3% of admissions in general health-care facilities.[15] The disease occurs most frequently in young, previously healthy individuals or in the context of one predisposing disease.[16] Acute kidney injury complicates malaria in 1–5% of cases, with incidences of up to 60% in patients with heavy parasitaemia or HIV/AIDS.[17] 20–85% of patients with leptospirosis[18] and 3·3–10·8% of adults and 0·9% of children admitted with dengue haemorrhagic fever and dengue shock syndrome[19] develop acute kidney injury. Haemorrhagic fever associated with hantavirus and acute kidney injury are also common in parts of Asia and Latin America.[20]

Two prospective studies[21,22] from India suggested that incidence of acute kidney injury was 5–9% in inpatient wards and 25–36% in paediatric intensive-care units in 2008 and 2010. 69 (2%) of 4015 children were treated for 70 episodes of acute kidney injury (17·4 cases per 1000 children) in a teaching hospital in Nigeria between July, 2010, and July, 2012, which was evident on admission in 58 children (83%) and confirmed in the RIFLE failure category for 49 children (70%).[23]

Causes

Overview

The causes of acute kidney injury are traditionally grouped into three categories: prerenal, renal (with direct intrinsic kidney damage), and postrenal. In prerenal disease, renal hypoperfusion leads to a decreased glomerular filtration rate as an adaptive response to various extrarenal insults such as volume depletion, systemic hypotension, significant renal vascular stenosis or thrombosis, severe systolic or diastolic cardiac failure, and activation of the neurohumoral axis increasing renal vascular resistance (eg, hepatorenal syndrome).[24] Postrenal failure occurs after obstruction of the urinary tract. By contrast with intrinsic acute kidney injury, timely reversion of prerenal or postrenal causes usually results in prompt recovery of function, but late correction can lead to kidney damage.

Intrinsic acute kidney injury includes acute, often rapidly progressive glomerulopathies, acute vasculitis, acute interstitial nephritis, and acute tubular necrosis.[3] Although acute tubular necrosis is the most frequent cause of intrinsic acute kidney injury, in absence of a kidney biopsy, it is often a presumptive diagnosis.

High-income countries

Acute tubular necrosis results from a variable mix of pathophysiological changes, and often occurs after one or more insult, including renal ischaemia from hypoperfusion after surgery, bleeding, dehydration, shock, or sepsis, toxic effects from drugs (often polypharmacy, radiocontrast drugs, poison, or trace elements), and pigment injury from myoglobin or haemoglobin.

Sepsis-induced acute kidney injury occurs from a complex mix of vascular and glomerular thrombotic processes, shock, hypotension with systemic fluid redistribution, and inflammation.[25] Most patients with sepsis are very ill, have multiorgan failure, and need complex therapeutic interventions. Other forms of parenchymatous acute kidney injury are attributable to tumour invasion or thrombotic microangiopathy.

Low-income and tropical countries

The pattern of hospital-acquired acute kidney injury occurring in high-level tertiary hospitals in some of the largest cities in these countries might be equivalent to that in high-income countries.

In more rural or deprived areas with poor health-system infrastructure, acute kidney injury will usually be a community-acquired disease, affecting young and previously healthy individuals.[26] The disease is frequently attributable to one cause (diarrhoeal or tropical infectious diseases, haemolytic uraemic syndrome, or acute post-infectious glomerulonephritis).[23,27] Other causes include postsurgical complications, snake bites, and intake of traditional and nephrotoxic medicines.[27]

Patients with HIV/AIDS can develop acute kidney injury in association with infections, hypovolaemia, and use of nephrotoxic antiretroviral drugs.[28] Drug-induced haemolysis can occur with deficiency of glucose-6-phosphate dehydrogenase, which is frequent (15–20%) in east Africa and Nigeria.

Although rates have declined, obstetric acute kidney injury accounts for 7–52% of the disease because of sub-optimum antenatal care and unsafe delivery practices.[29] Acute kidney injury in the first trimester is associated with

	Cases
Infections	92 (55%)
Pneumonia	24 (14%)
Diarrhoea	13 (8%)
Sepsis	13 (8%)
Dengue	10 (6%)
Scrub typhus	3 (2%)
Leptospirosis	1 (1%)
Malaria	1 (1%)
Acute glomerular diseases	28 (17%)
Underlying renal diseases	10 (6%)
Underlying cardiac diseases	8 (5%)
Envenomations	7 (4%)
Haemolytic uraemic syndrome	6 (4%)
Drugs	2 (1%)
Others*	13 (8%)

Data from Krishnamurthy and colleagues.[21] *Includes children with hepatorenal syndrome, diabetic ketoacidosis, hypoxic ischaemic injury, acute lymphoblastic leukaemia, intracranial haemorrhage with shock, and poisonings (organophosphorus and endosulfan).

Table: **Most important causes of 166 cases of paediatric acute kidney injury in South India**

sepsis or haemorrhage after abortion, whereas in the third trimester it can occur in the context of puerperal sepsis, pre-eclampsia or eclampsia, or post-partum haemorrhage.

Epidemics of acute kidney injury develop after outbreaks of severe gastroenteritis (eg, typhus or cholera) or leptospirosis after flooding. Incidence of specific diseases leading to acute kidney injury varies seasonally and, during times of peak incidence, local health resources can be overwhelmed and more patients will develop the disease, often as a result of acute glomerular disease after infection[16] or after volume depletion. Epidemics of acute kidney injury can also occur after disasters, such as earthquakes or hurricanes and are largely attributable to rhabdomyolysis resulting in crush syndrome.[30]

Venomous snake bites account for a notable proportion of patients with acute kidney injury in India, Burma, and Thailand. Exposure to industrial chemicals, including copper sulphate used in the leather industry and formic acid in rubber manufacturing, are causes of acute kidney injury that are usually restricted to tropical areas.[27] Traditional remedies made from plant toxins and indigenous delicacies such as djenkol beans and mushrooms lead to acute kidney injury in Africa and southeast Asia. Renal stones are a key cause of obstructive uropathy in northeast Africa and western Asia.

Although incidence is declining, volume depletion caused by diarrhoea contributes substantially to acute kidney injury in children in low-income countries.[31] Haemolytic uraemic syndrome associated with shigellosis and shigatoxin-producing *Escherichia coli* is an important cause of acute kidney injury in children worldwide.[16] Glomerulonephritis after infection is declining in most regions but is an important cause of paediatric acute kidney injury.[16]

Infection was the most common cause of paediatric acute kidney injury in a tertiary hospital in southern India between June, 2010, and March, 2011, but non-communicable diseases and drug use were also notable factors (table).[21] In Nigeria, primary kidney disease (39%; mostly acute glomerulonephritis and nephrotic syndrome), sepsis (26%), and malaria (11%) were the most common causes of acute kidney injury.[23]

Accidental contamination of drugs can lead to epidemics of paediatric deaths from acute kidney injury, such as occurred with diethylene glycol contamination of cough and fever drugs in Haiti between November, 1995, and May, 1996.[32]

Risk factors

Several comorbidities, including diabetes mellitus, cardiovascular disease, chronic liver disease, cancer, and complex surgery have been associated with development of acute kidney injury in community, hospital, and critical care settings.[8,33]

Crush syndrome is a reperfusion injury that occurs after ischaemia of skeletal muscle caused by prolonged continuous pressure. After release from the pressure, severe volume depletion and circulatory failure can develop, leading to large amounts of myoglobin and potassium being released into the circulation and resultant acute tubular injury and hyperkalaemia[34]

Pre-existing chronic kidney disease, either manifesting as reduced estimated glomerular filtration rate or proteinuria, is one of the most potent risk factors for acute kidney injury.[35,36] Volume depletion, especially in very young individuals and the elderly is an important common risk factor.

Pathophysiology

About two-thirds of acute tubular necrosis is caused by renal ischaemia-reperfusion injury or sepsis, and a third is caused by direct or indirect nephrotoxicity. Tubular and vascular changes, alongside interstitial inflammation, are responsible for the acute decrease in glomerular filtration rate.

Pathophysiological mechanisms of acute kidney injury, including molecular and cellular mechanisms have been described in several reviews.[37,38] The disease also has distant effects on the cardiovascular, respiratory, hepatic, and neurological systems.[39]

The kidney has a striking capacity for recovery after injury,[37,38] and elucidation of the mechanisms responsible for this regenerative process could lead to the development of new treatments that hasten recovery. Although the repair process for mild injury is normal and restores the renal structure, when the injury is more severe (or is superimposed on baseline kidney abnormalities), the repair process can lead to fibrosis, which can increase risk of progression to chronic kidney disease.[40]

Clinical approaches

Diagnosis

Causal diagnosis of acute kidney injury relies on a combination of a patient's history, clinical examination, assessment of kidney function, renal imaging, renal biopsy and, potentially, measurement of biomarkers of structural damage.[3]

After diagnosis and management of life-threatening complications, such as hyperkalaemia, intractable volume overload, severe acidosis, and uraemic serositis, a diagnosis of post-obstructive acute kidney injury should first be excluded by imaging of the kidney and urinary tract by ultrasound or CT without contrast. Although presence of small kidneys is suggestive of chronic kidney damage, it does not exclude acute on chronic kidney injury.

After exclusion of post-obstructive acute kidney injury, an assessment of the patient's volume status should be made to determine the need for eventual volume repletion. Volume depletion is best identified by a history of fluid loss, severe postural hypotension, dizziness, and a large pulse rate change (>30 beats per min) on standing at clinical examination.

In severely ill patients, assessment of fluid responsiveness requires small boluses of fluid (eg, 500 mL of isotonic saline in 30 min), followed by assessment of cardiac output parameters. Static haemodynamic parameters, including central venous pressure and pulmonary artery occlusion pressure do not predict fluid responsiveness. Dynamic testing requires monitoring of the changes in stroke volume during mechanical ventilation or after a passive leg-raising manoeuvre.[41] Fluid challenge should however not result in fluid loading.[42] Patients need to have urine output monitored and volume replacement should be stopped when oliguria persists.[43]

Whereas a low fractional excretion of sodium suggests that an episode of acute kidney injury is probably transient rather than persistent, this finding does not exclude significant tubular injury in other nephrons.[44] A low fractional excretion might also occur in the presence of septic and other forms of renal acute kidney injury;[44] a high value of sodium is unhelpful after diuretic administration.

New biomarkers might be able to detect renal cellular damage and allow detection of acute kidney injury up to 48 h earlier than could an increase in serum creatinine.[45,46] Such biomarkers could assist in detection of the presence of structural injury in cases that were previously assumed to represent purely functional changes.[44] One large meta-analysis of observational studies in critically ill patients[47] and a large multicentre prospective study of patients admitted through the emergency department[48] have identified a category of patients who are biomarker positive but creatinine negative, suggesting the presence of renal damage without an increase in serum creatinine. Notably, this pattern was associated with an increased need for early dialysis or in-hospital mortality, suggesting that the presence of renal damage without an increase in creatinine, might signify at least short-term adverse outcomes. Although the area of biomarkers is evolving rapidly, routine application is not yet recommended because their added value to clinical models is not well established.[49]

Urine analysis of protein and sediment under light microscopy, leading to the detection of white blood cells and red blood cells, tubular epithelial cells, casts, or crystals, can assist the differential diagnosis.[50] Increased renal resistance on Doppler ultrasound is a sign of structural kidney damage, but is operator dependent. Contrast-enhanced ultrasonography might assist assessment of regional renal perfusion.

Finally, the time and place of renal biopsy depends on the clinical context, but is helpful for exclusion of rapidly progressive glomerulonephritis, vasculitis, and interstitial nephritis, and should be undertaken promptly if these disorders are suspected.

Prevention and management

Non-dialytic management

Identification and correction of potentially reversible causes of kidney damage such as volume depletion and avoidance of nephrotoxins are of paramount importance. Drug doses should be adjusted on the basis of assessment of renal function, preferably with timed urinary clearances.[51] Iodine, and to a lesser extent, gadolinium contrast media are potentially nephrotoxic and should be avoided when possible. The preventive and eventual therapeutic role of volume expansion, diuretics, vasoactive drugs, growth factors, and antioxidants has been widely studied, and some clinical trials showed beneficial results. However, many of these studies have methodological problems and the results obtained in a specific setting cannot always be extrapolated to other disorders (eg, hospital-acquired *vs* community-acquired disease or acute kidney injury caused by one cause *vs* disease caused by a multisystem disorder, such as sepsis).

Provision of fluid resuscitation, blood products, inotropes, and early antibiotics is key to reduce the number of deaths that occur from septic shock.[52] Despite a number of randomised controlled trials comparing colloids with crystalloids for fluid resuscitation,[53,54] no consensus has been reached. Crystalloids should be preferred to colloids at least in very ill patients because the more expensive colloids have shown evidence of apparent harm and no clear benefit.[55]

Monitoring for metabolic acidosis is recommended when hyperchloraemic saline solutions such as 0·9% saline (chloride 150 mmol/L) are used. High-chloride solutions seem to be associated with more acute kidney injury than are low-chloride solutions.[56]

Adequate hydration before and after a contrast-enhanced scan, and continued for 24 h if possible, is recommended in patients who are at risk for contrast-induced acute kidney injury.[6] Isotonic saline was reported

to be superior to isotonic bicarbonate.[57] Noradrenaline is the first-line strategy when blood volume has been restored and vasoactive drugs are needed to restore or maintain perfusion pressure.[42]

At present, no evidence exists to suggest that acetylcysteine helps prevent contrast-induced acute kidney injury.[6] A long list of pharmacological drugs—including diuretics, renal dose dopamine, fenoldopam, atrial natriuretic peptide, insulin growth factor, statins, calcium-channel blockers, and adenosine antagonists—did not consistently improve renal function in acute kidney injury.[6]

Intensive insulin therapy to maintain normal blood glucose concentrations in patients in intensive care reduced rates of postoperative acute kidney injury requiring RRT,[58] but these benefits were not confirmed in multicentre studies[59] and spontaneous or insulin-induced moderate and severe hypoglycaemia is associated with an increased risk of death, especially after distributive shock.[60]

Although preventive strategies for acute kidney injury in low-income countries are essentially the same as in high income countries, they pose additional and unique ethical problems. Because health care is affected by social and economic factors, any intervention needs to address all health determinants, including educational, economic, and environmental factors.[61] Expensive interventions to prevent or treat acute kidney injury could affect the ability of a health-care system to meet other needs. Conversely, the high mortality associated with primary diseases such as malaria and HIV/AIDS is frequently caused by serious acute kidney injury that cannot be treated because of a lack of dialysis facilities.[62] Because of the scarcity of resources and the presence of overwhelming health-related and other problems in these countries, prevention of acute kidney injury ought to target eradication of the most common causes (ie, tropical and non-tropical infections), improve education and socioeconomic statuses, and support health-care structures and access. In rural centres, primary-care physicians need to be able to treat common causes of acute kidney injury and to transfer individuals requiring critical care at the right time to hospitals with secondary and tertiary capacity to deal with acute kidney injury, including RRT.[61] Innovative strategies, such as outreach programmes, improved transportation, involvement of community health workers, and strengthening of first-level health units, are needed to decrease the physical barriers to access of health services by marginalised populations.

Special attention needs to be given to promotion of planned pregnancies with appropriate antenatal care by skilled midwives. Overall, most preventive efforts should focus at the primary health-care level.

Because mass disasters cannot be predicted, they often overwhelm local health-care systems, even in high-income countries. Such events necessitate careful advance planning and education and can need complex logistic measures once the disaster occurs. The Renal Disaster Relief Task Force of the International Society of Nephrology formulated comprehensive recommendations on how to react practically in difficult conditions.[63]

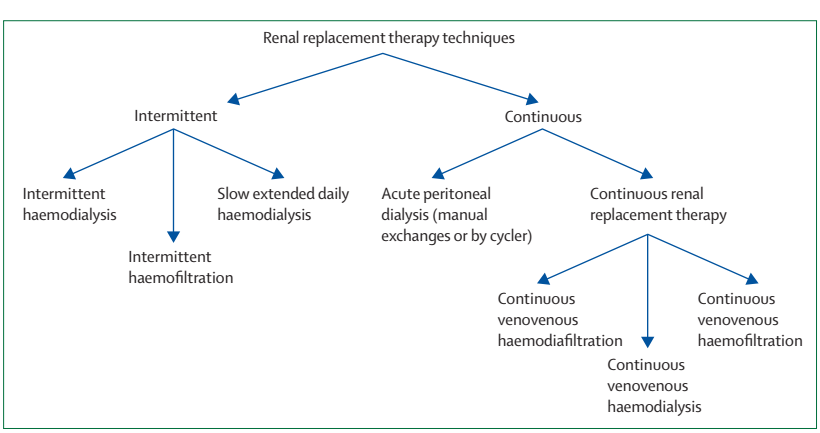

Figure 1: **Approaches to renal replacement therapy in acute kidney injury**

Dialytic management

In the absence of life-threatening complications, timing of initiation of RRT is a matter of debate.[64] A systematic review suggested that early institution of such therapy in severely ill patients with acute kidney injury might improve survival,[65] but was based on heterogeneous studies of varying quality and unclear definitions of early dialysis. In the absence of strong evidence, a definitive recommendation on timing of RRT cannot be made.

Various techniques for RRT, either intermittent or continuous, are available for patients with acute kidney injury (figure 1). Intermittent haemodialysis is less expensive than is continuous RRT and has similar efficacy.[66] For indicated patients, haemodialysis can be done daily and run for extended treatment times (6–10 h), called slow low-efficiency daily dialysis (SLEDD). SLEDD is associated with a substantial reduction in cost.[67] Although the logistical issues surrounding the use of intermittent haemodialysis and SLEDD probably differ around the world, they are typically provided by haemodialysis nurses under the supervision of a nephrologist, unlike continuous RRT, which can be delivered by intensive-care unit nursing staff.

Several randomised controlled trials show equivalent outcomes with intermittent haemodialysis and continuous RRT[68] and the choice of intermittent or continuous therapy is presently based on local experience and availability of therapies. Ideally, the dialysis prescription (blood and dialysate flow, dialysate composition and temperature, ultrafiltration rate, and anticoagulation strategy) should be tailored to the patient's needs, which can change daily in very ill patients. Continuous RRT techniques have been associated with improved renal recovery.[69] Initial studies that reported benefit from high-dose continuous RRT (35 mL/kg per h)[70] have not been confirmed[71] and present guidelines recommend prescription of a continuous RRT

dose of 25 mL/kg per h to provide an effective dose of at least 20 mL/kg per h.[6]

For intermittent haemodialysis, the Acute Renal Failure Trial Network trial[72] of more than 1100 patients did not show a difference in mortality between daily versus alternate daily dialysis, provided the duration of each session was long enough for smooth ultrafiltration.[73] In most studies with intermittent haemodialysis, dose of dialysis was based on clearance of small molecules and did not include fluid balance.[73] Another finding, based on the RENAL trial[74] suggesting survival was improved through maintenance of a negative fluid balance, needs to be assessed in prospective randomised controlled trials. When intensive regimens are used, drug doses, such as of antibiotics, need to be adjusted.[75]

In high-income countries, acute peritoneal dialysis is rarely used in severely ill adult patients with acute kidney injury (who often also have sepsis). This strategy is different in young children and in low-income countries, when peritoneal dialysis is easier to start than extracorporeal techniques because of its technical simplicity and equipment shortages.[16] Three randomised controlled trials compared acute peritoneal dialysis with haemodialysis modalities in patients with acute kidney injury. Phu and colleagues[76] reported significantly shortened survival in patients treated with acute peritoneal dialysis compared with haemofiltration, but the study used rigid peritoneal catheters, an open system with manual exchanges, short dwell times, and an acetate-based dialysate, produced by the hospital pharmacy. Two other trials reported similar survival between peritoneal dialysis and daily intermittent haemodialysis[77] and continuous venovenous haemodiafiltration.[78] The Sustainable Kidney Care Foundation, together with industry, universities, and funding organisations, tries to establish peritoneal dialysis programmes for acute kidney injury in African countries with a special focus on treatment of children and women of childbearing age.[79]

Prognosis

Acute kidney injury is associated with several complications, including fluid overload, electrolyte abnormalities, and coagulopathy. Fluid overload is associated with increased risk of death,[80,81] although this association might also reflect severity of illness. Acute kidney injury exerts direct effects on other organs and systems, and contributes to multiorgan failure in critically ill patients.[39] Although the severity and outcome of an episode of acute kidney injury are predicted by its duration,[82] even transient disease is associated with increased mortality.[44] Acute kidney injury that requires dialysis in critically ill patients is associated with a mortality of 40–70% and the disease itself is an independent risk factor for death.[71,72]

Health-related quality of life in survivors of acute kidney injury is very variable, but 62–77% of patients reported a good or an excellent health status in one study.[83] Conversely, a low overall health utilities index 60 days after the onset of acute kidney injury has been reported, suggesting compromised health utility,[84] and patients with worse health-related quality of life had an increased risk of death at 1 year.[85]

The established perception that patients who recover from acute kidney injury return to (or approach) normal baseline kidney function has recently been questioned. A meta-analysis of 13 cohort studies[86] showed that patients with acute kidney injury had a higher hazard for development of new-onset chronic kidney disease. This risk was especially prevalent in patients with acute or pre-existing chronic kidney disease. Normalisation of serum creatinine is however not automatically equivalent to complete recovery of renal function, but could also suggest hyperfunction of uninjured nephrons or a decline in creatinine generation by muscle wasting after an acute illness. With this caveat in mind, some investigators have suggested that acute kidney injury is a risk factor for de-novo chronic or end-stage kidney disease in patients without preceding chronic disease and in whom kidney function seems to completely recover after hospital-associated acute kidney injury. Bucaloiu and colleagues[87] observed de-novo chronic kidney disease with an incidence of 28·1 cases per 1000 patient-years in patients with reversible acute kidney injury compared with 13·1 cases per 1000 patient-years in propensity-matched controls (figure 2), which was associated with increased mortality. Jones and colleagues[88] also reported an association with increased risk of development of incident stage 3 chronic kidney disease.

A substantial risk of long-term renal sequelae is associated with paediatric acute kidney injury caused by intrinsic kidney diseases, such as Henoch-Schönlein purpura or haemolytic uraemic syndrome.[89,90] The long-term renal prognosis of acute kidney injury not caused by primary kidney disease in children is largely unknown but about 10% of tertiary-care paediatric patients in intensive-care units who survived acute kidney injury and recovered normal renal function developed chronic kidney disease after 1–3 years in one study.[91] The burden of chronic kidney disease in this population might be increased with additional follow-up.

Such results reinforce the need for long-term medical follow-up of paediatric and adult survivors of acute kidney injury, even after almost complete return to baseline kidney function. However, at present few at-risk survivors of acute kidney injury are seen by a nephrologist during the first year of discharge.[92]

The fact that even silent episodes of acute kidney injury can contribute to the development or progression of chronic kidney disease has striking socioeconomic and public health effects, not least in low-income countries where individuals are already at risk for chronic disease because of low birthweight or poor nutrition. Furthermore, in view of the known association of end-stage and

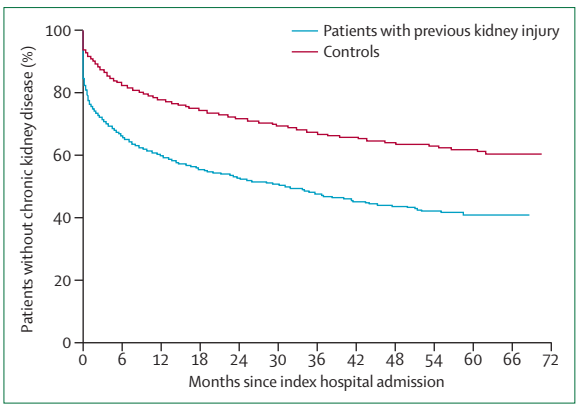

Figure 2: **Cumulative incidence of chronic kidney disease by exposure status (recovered acute kidney injury group *vs* controls) in patients with normal baseline kidney function**
Reproduced with permission from Bucaloiu and colleagues.[87]

chronic kidney disease with cardiovascular comorbidity, how additional survival from acute kidney injury that requires chronic dialysis will increase the burden of cardiovascular disease is unknown. For example, in a cohort of 408 children requiring dialysis in intensive-care units in Brazil, 12% of 107 survivors were dialysis-dependent after 3 months.[93] Moreover, for another 84 survivors of acute kidney injury, only 64% had an estimated glomerular filtration rate of more than 60 mL/min per 1·73 m² at 18 months, with 7% dying and 5% having end-stage renal disease after 2·5–7·5 years.[94] Residual renal impairment with abnormal creatinine, hypertension, haematuria, or proteinuria was noted in six (38%) of 16 children followed up for 10 years after acute kidney injury in India.[95]

Costs

Existing studies about costs associated with acute kidney injury are restricted to calculations of the costs of procedures and early admission to hospitals but did not include long-term costs. Costs attributable to acute kidney injury increase as the definition broadens and with the severity of the disease. Data from 23 hospitals in MA, USA,[96] in 2 years show that acute kidney injury, compared with non-acute injury, resulted in higher hospital resource use, with median direct hospital costs increase by US$2600 and hospital length of stay by 5 days. The additional costs attributed to in-hospital acute kidney injury determined in one Boston hospital in 2005, ranged from $13 200 for a greater than 44·2 µmol/L change in serum creatinine to $33 161 for a 176·8 µmol/L change.[4] Similarly, in a study of acute kidney injury after cardiac surgery, even RIFLE-renal risk disease was associated with a 1·6-fold increase in total postoperative costs compared with controls.[97] The costs for acute kidney injury requiring dialysis in high-income countries are setting-dependent and vary widely between centres, but are generally greatest for continuous RRT.[98]

The overall health-care costs and consequences of acute kidney injury that develops into chronic and end-stage disease have not been well quantified. Extrapolation from Wald and colleagues' study[99] suggests that acute kidney injury-precipitated chronic kidney disease could account for 3% of the annual incidence of end-stage renal disease in the USA.[100]

Finally, scant information exists about costs of health care for acute kidney injury in developing countries. Direct hospital costs for 231 children with haemolytic uraemic syndrome in Buenos Aires, Argentina in 1987–2003[101] were estimated at $15 400, with indirect costs accounting for an additional $7355 per patient.

Because of direct effects of acute kidney injury on productivity, indirect costs are difficult to define. For example, only 19 (28%) of 68 patients with severe disease in Brazil could return to their jobs 3–12 months after hospital discharge.[93]

Conclusions

Although our understanding of the causes and mechanisms of acute kidney injury is improving, the disease's occurrence and short-term and long-term complications are difficult to prevent. These problems impose an enormous socioeconomic burden, especially in low-income countries. An important concern is that even small acute changes in kidney function can lead to complications, chronic kidney disease, end-stage renal disease, and death. A concerted multinational and multidisciplinary effort is needed to enable early recognition and management of this devastating disease. We encourage international and national nephrological societies through their educational programmes to collaborate with international institutions (eg, WHO), governments, and non-profit organisations to detect and reduce the risk factors for acute kidney injury, especially in low-income regions. Besides improvement of overall health care in every country, relatively straightforward, low-cost (but accurate) techniques for determination of serum creatinine and urinary albumin should be available to health-care providers. Before introduction of expensive diagnostic techniques such as new biomarkers in low-income countries, training in accurate reading of a urinary sediment test and techniques for bedside assessment of the patient's volume status should be provided, and acute peritoneal dialysis should be recommended as the first-choice dialysis technique.

Future perspectives

The definition of acute kidney injury needs to be standardised in clinical trials through implementation of an international definition and classification, as proposed by the recently published KDIGO acute kidney injury guideline group.

Multinational epidemiological studies are needed to assess incidence, prevalence, and causes of acute kidney

injury, especially in low-income countries. Databases generated should include traditional markers of kidney function and new serum and urinary biomarkers of damage to refine the definition of acute kidney injury and facilitate therapeutic trials. Moreover, potentially preventable causes of acute kidney injury need to be explored in different age groups and settings (eg, prevention or prompt management of tropical infectious diseases and improvement of prenatal care). Genome-wide association studies are also needed to determine risk of acute kidney injury in different settings and with respect to long-term outcomes. Whether small rises in serum creatinine correspond to low stages of acute kidney injury, and whether such staging is truly determinant of short-term and long-term outcomes, needs to be assessed.

Long-term outcomes of new treatment approaches, based on new pathophysiological ideas (eg, induction of kidney repair and kidney tissue regeneration) will be needed to improve treatment options. Furthermore, research is needed into the development of alternative extracorporeal renal replacement options (including acute peritoneal dialysis) that need less or no water, and less or no network electricity.

The effect of acute intermittent so-called kidney attacks on the evolution of chronic kidney disease should be assessed in both children and adults in high-income and low-income countries

Contributors

NHL wrote the first draft and revised the report in close cooperation with RV and WVB. All other authors commented on different sections of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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