



Global Kidney Disease 2

Acute kidney injury: an increasing global concern

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Lancet 2013; 382: 170–79

Published Online

May 31, 2013

[http://dx.doi.org/10.1016/S0140-6736\(13\)60647-9](http://dx.doi.org/10.1016/S0140-6736(13)60647-9)

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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.

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,

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

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 leptospirosis¹⁸ and 3·3–10·8% of adults and 0·9% of children admitted with dengue haemorrhagic fever and dengue shock syndrome¹⁹ 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 neuro-humoral 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 infection¹⁶ 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 patients⁴⁷ and a large multicentre prospective study of patients admitted through the emergency department⁴⁸ 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 studies⁵⁹ 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

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 RRT⁶⁸ 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 confirmed⁷¹ and present guidelines recommend prescription of a continuous RRT

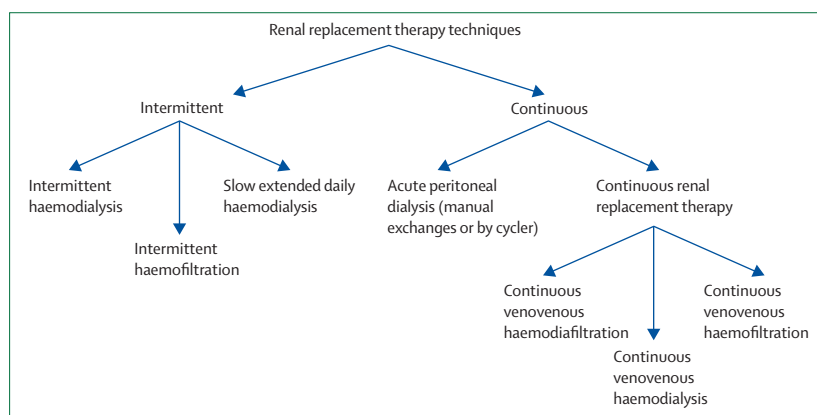


Figure 1: Approaches to renal replacement therapy in acute kidney injury

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 trial⁷² 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 trial⁷⁴ 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 colleagues⁷⁶ 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 haemodialysis⁷⁷ 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 studies⁸⁶ 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 colleagues⁸⁷ 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 colleagues⁸⁸ 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

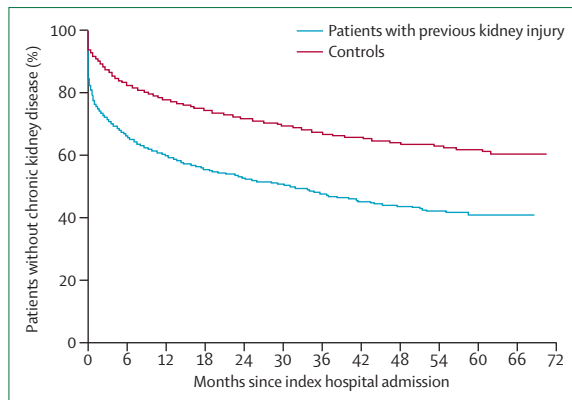


Figure 2: Cumulative incidence of chronic kidney disease by exposure status (recovered acute kidney injury group vs controls) in patients with normal baseline kidney function

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' study⁹⁹ 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 1987–2003¹⁰¹ 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.

References

- Liaño F, Pascual J, and the Madrid Acute Renal Failure Study Group. Epidemiology of acute renal failure: a prospective, multicenter, community-based study. *Kidney Int* 1996; **50**: 811–18.
- Uchino S, Kellum JA, Bellomo R, et al, and the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005; **294**: 813–18.
- Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet* 2012; **380**: 756–66.
- Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; **16**: 3365–70.
- Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol* 2004; **15**: 1597–605.
- Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. *Kidney Int Suppl* 2012; **2**: 1–138.
- Wlodzimirow KA, Abu-Hanna A, Slabbekoorn M, Chamuleau RA, Schultz MJ, Bouman CS. A comparison of RIFLE with and without urine output criteria for acute kidney injury in critically ill patients. *Crit Care* 2012; **16**: R200.
- Ali T, Khan I, Simpson W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol* 2007; **18**: 1292–98.
- Waikar SS, Curhan GC, Wald R, McCarthy EP, Chertow GM. Declining mortality in patients with acute renal failure, 1988 to 2002. *J Am Soc Nephrol* 2006; **17**: 1143–50.
- Xue JL, Daniels F, Star RA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. *J Am Soc Nephrol* 2006; **17**: 1135–42.
- Amin AP, Salisbury AC, McCullough PA, et al. Trends in the incidence of acute kidney injury in patients hospitalized with acute myocardial infarction. *Arch Intern Med* 2012; **172**: 246–53.
- Joannidis M, Metnitz B, Bauer P, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med* 2009; **35**: 1692–702.
- Goldstein SL. Acute kidney injury in children and its potential consequences in adulthood. *Blood Purif* 2012; **33**: 131–37.
- Adhikari NK, Rubenfeld GD. Worldwide demand for critical care. *Curr Opin Crit Care* 2011; **17**: 620–25.
- Naicker S, Aboud O, Gharbi MB. Epidemiology of acute kidney injury in Africa. *Semin Nephrol* 2008; **28**: 348–53.
- Cerdá J, Bagga A, Kher V, Chakravarthi RM. The contrasting characteristics of acute kidney injury in developed and developing countries. *Nat Clin Pract Nephrol* 2008; **4**: 138–53.
- Mishra SK, Das BS. Malaria and acute kidney injury. *Semin Nephrol* 2008; **28**: 395–408.
- Andrade L, de Francesco Daher E, Seguro AC. Leptospirosis nephropathy. *Semin Nephrol* 2008; **28**: 383–94.
- Mehra N, Patel A, Abraham G, Reddy YN, Reddy YN. Acute kidney injury in dengue fever using Acute Kidney Injury Network criteria: incidence and risk factors. *Trop Doct* 2012; **42**: 160–62.
- Clement J, Maes P, Lagrou K, Van Ranst M, Lameire N. A unifying hypothesis: hantavirus disease. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 1–5.
- Krishnamurthy S, Mondal N, Narayanan P, Biswal N, Srinivasan S, Soundravally R. Incidence and etiology of acute kidney injury in southern India. *Indian J Pediatr* 2013; **80**: 183–89.
- Mehta P, Sinha A, Sami A, et al. Incidence of acute kidney injury in hospitalized children. *Indian Pediatr* 2012; **49**: 537–42.
- Esezobor CI, Ladapo TA, Osinaike B, Lesi FE. Paediatric acute kidney injury in a tertiary hospital in Nigeria: prevalence, causes and mortality rate. *PLoS One* 2012; **7**: e51229.
- Blantz RC, Singh P. Analysis of the prerenal contributions to acute kidney injury. *Contrib Nephrol* 2011; **174**: 4–11.
- Jacobs R, Honore PM, Joannes-Boyau O, et al. Septic acute kidney injury: the culprit is inflammatory apoptosis rather than ischemic necrosis. *Blood Purif* 2011; **32**: 262–65.
- Li PK, Burdmann EA, Mehta RL. Acute kidney injury: global health alert. *Kidney Int* 2013; **83**: 372–76.
- Mathew AJ, George J. Acute kidney injury in the tropics. *Ann Saudi Med* 2011; **31**: 451–56.
- Cohen SD, Chawla LS, Kimmel PL. Acute kidney injury in patients with human immunodeficiency virus infection. *Curr Opin Crit Care* 2008; **14**: 647–53.
- Bentata Y, Housni B, Mimouni A, Azzouzi A, Abouqal R. Acute kidney injury related to pregnancy in developing countries: etiology and risk factors in an intensive care unit. *J Nephrol* 2012; **25**: 764–75.
- Sever MS, Ereik E, Vanholder R, et al. Lessons learned from the catastrophic Marmara earthquake: factors influencing the final outcome of renal victims. *Clin Nephrol* 2004; **61**: 413–21.
- Cerdá J, Lameire N, Eggers P, et al. Epidemiology of acute kidney injury. *Clin J Am Soc Nephrol* 2008; **3**: 881–86.
- O'Brien KL, Selanikio JD, Hecdivert C, et al, and the Acute Renal Failure Investigation Team. Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. *JAMA* 1998; **279**: 1175–80.
- Cruz DN, Ronco C. Acute kidney injury in the intensive care unit: current trends in incidence and outcome. *Crit Care* 2007; **11**: 149.
- Vanholder R, Sever MS, Ereik E, Lameire N. Rhabdomyolysis. *J Am Soc Nephrol* 2000; **11**: 1553–61.
- James MT, Hemmelgarn BR, Wiebe N, et al, and the Alberta Kidney Disease Network. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. *Lancet* 2010; **376**: 2096–103.
- Lafrance JP, Djurdjev O, Levin A. Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort. *Nephrol Dial Transplant* 2010; **25**: 2203–09.

- 37 Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. *J Clin Invest* 2011; **121**: 4210–21.
- 38 Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. *Nat Rev Nephrol* 2011; **7**: 189–200.
- 39 Grams ME, Rabb H. The distant organ effects of acute kidney injury. *Kidney Int* 2012; **81**: 942–48.
- 40 Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney Int* 2012; **82**: 516–24.
- 41 Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. *Ann Intensive Care* 2011; **1**: 1.
- 42 Vincent JL, De Backer D. ICU nephrology: the implications of cardiovascular alterations in the acutely ill. *Kidney Int* 2012; **81**: 1060–66.
- 43 Macedo E, Malhotra R, Claure-Del Granado R, Fedullo P, Mehta RL. Defining urine output criterion for acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2011; **26**: 509–15.
- 44 Nejat M, Pickering JW, Devarajan P, et al. Some biomarkers of acute kidney injury are increased in pre-renal acute injury. *Kidney Int* 2012; **81**: 1254–62.
- 45 Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2005; **365**: 1231–38.
- 46 Endre ZH, Pickering JW, Walker RJ. Clearance and beyond: the complementary roles of GFR measurement and injury biomarkers in acute kidney injury (AKI). *Am J Physiol Renal Physiol* 2011; **301**: F697–707.
- 47 Haase M, Devarajan P, Haase-Fielitz A, et al. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. *J Am Coll Cardiol* 2011; **57**: 1752–61.
- 48 Nickolas TL, Schmidt-Ott KM, Canetta P, et al. Diagnostic and prognostic stratification in the emergency department using urinary biomarkers of nephron damage: a multicenter prospective cohort study. *J Am Coll Cardiol* 2012; **59**: 246–55.
- 49 Endre ZH, Pickering JW, Walker RJ, et al. Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. *Kidney Int* 2011; **79**: 1119–30.
- 50 Perazella MA, Parikh CR. How can urine microscopy influence the differential diagnosis of AKI? *Clin J Am Soc Nephrol* 2009; **4**: 691–93.
- 51 Bouchard J, Macedo E, Soroko S, et al, and the Program to Improve Care in Acute Renal Disease. Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury. *Nephrol Dial Transplant* 2010; **25**: 102–07.
- 52 Jones AE, Brown MD, Trzeciak S, et al, and the Emergency Medicine Shock Research Network investigators. The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis. *Crit Care Med* 2008; **36**: 2734–39.
- 53 Myburgh JA, Finfer S, Bellomo R, et al, and the CHEST Investigators, and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; **367**: 1901–11.
- 54 Perner A, Haase N, Guttormsen AB, et al, and the 6S Trial Group, and the Scandinavian Critical Care Trials Group. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; **367**: 124–34.
- 55 Shaw AD, Kellum JA. The risk of AKI in patients treated with intravenous solutions containing hydroxyethyl starch. *Clin J Am Soc Nephrol* 2013; **8**: 497–503.
- 56 Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; **308**: 1566–72.
- 57 Klima T, Christ A, Marana I, et al. Sodium chloride vs. sodium bicarbonate for the prevention of contrast medium-induced nephropathy: a randomized controlled trial. *Eur Heart J* 2012; **33**: 2071–79.
- 58 van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359–67.
- 59 Finfer S, Chittock DR, Su SY, et al, and the NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**: 1283–97.
- 60 Finfer S, Liu B, Chittock DR, et al, and the NICE-SUGAR Study Investigators. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med* 2012; **367**: 1108–18.
- 61 De Maeseneer J, Flinkenflögel M. Primary health care in Africa: do family physicians fit in? *Br J Gen Pract* 2010; **60**: 286–92.
- 62 Carter M, Callegari J. Proposed treatment program for acute renal failure (ARF) in the United Republic of Tanzania as a model for sub-Saharan Africa. *J Hosp Mark Public Relations* 2007; **18**: 81–88.
- 63 Sever MS, Vanholder R, and the RDRTF of ISN Work Group on Recommendations for the Management of Crush Victims in Mass Disasters. Recommendation for the management of crush victims in mass disasters. *Nephrol Dial Transplant* 2012; **27** (suppl 1): i1–67.
- 64 Macedo E, Mehta RL. When should renal replacement therapy be initiated for acute kidney injury? *Semin Dial* 2011; **24**: 132–37.
- 65 Karvellas CJ, Farhat MR, Sajjad I, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. *Crit Care* 2011; **15**: R72.
- 66 Manns B, Doig CJ, Lee H, et al. Cost of acute renal failure requiring dialysis in the intensive care unit: clinical and resource implications of renal recovery. *Crit Care Med* 2003; **31**: 449–55.
- 67 Schwenger V, Weigand MA, Hoffmann O, et al. Sustained low efficiency dialysis using a single-pass batch system in acute kidney injury—a randomized interventional trial: the RENAL Replacement Therapy Study in Intensive Care Unit PatiEnts. *Crit Care* 2012; **16**: R140.
- 68 Vanholder R, Van Biesen W, Hoste E, Lameire N. Pro/con debate: continuous versus intermittent dialysis for acute kidney injury: a never-ending story yet approaching the finish? *Crit Care* 2011; **15**: 204.
- 69 Srisawat N, Lawsin L, Uchino S, Bellomo R, Kellum JA, and the BEST Kidney Investigators. Cost of acute renal replacement therapy in the intensive care unit: results from The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study. *Crit Care* 2010; **14**: R46.
- 70 Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet* 2000; **356**: 26–30.
- 71 Bellomo R, Cass A, Cole L, et al, and the RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009; **361**: 1627–38.
- 72 Palevsky PM, Zhang JH, O'Connor TZ, et al, and the VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; **359**: 7–20.
- 73 Macedo E, Claure-Del Granado R, Mehta RL. Effluent volume and dialysis dose in CRRT: time for reappraisal. *Nat Rev Nephrol* 2012; **8**: 57–60.
- 74 Bellomo R, Cass A, Cole L, et al, and the RENAL Replacement Therapy Study Investigators. An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs Augmented Level of Replacement Therapy trial. *Crit Care Med* 2012; **40**: 1753–60.
- 75 Kielstein JT, Burkhardt O. Dosing of antibiotics in critically ill patients undergoing renal replacement therapy. *Curr Pharm Biotechnol* 2011; **12**: 2015–19.
- 76 Phu NH, Hien TT, Mai NT, et al. Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. *N Engl J Med* 2002; **347**: 895–902.
- 77 Gabriel DP, Caramori JT, Martim LC, Barretti P, Balbi AL. High volume peritoneal dialysis vs daily hemodialysis: a randomized, controlled trial in patients with acute kidney injury. *Kidney Int Suppl* 2008; **108**: S87–93.
- 78 George J, Varma S, Kumar S, Thomas J, Gopi S, Pisharody R. Comparing continuous venovenous hemodiafiltration and peritoneal dialysis in critically ill patients with acute kidney injury: a pilot study. *Perit Dial Int* 2011; **31**: 422–29.
- 79 Carter M, Kilonzo K, Odiit A, et al. Acute peritoneal dialysis treatment programs for countries of the East African community. *Blood Purif* 2012; **33**: 149–52.
- 80 Bouchard J, Soroko SB, Chertow GM, et al, and the Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009; **76**: 422–27.

- 81 Sutherland SM, Zappitelli M, Alexander SR, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. *Am J Kidney Dis* 2010; **55**: 316–25.
- 82 Brown JR, Kramer RS, Coca SG, Parikh CR. Duration of acute kidney injury impacts long-term survival after cardiac surgery. *Ann Thorac Surg* 2010; **90**: 1142–48.
- 83 Morgera S, Kraft AK, Siebert G, Luft FC, Neumayer HH. Long-term outcomes in acute renal failure patients treated with continuous renal replacement therapies. *Am J Kidney Dis* 2002; **40**: 275–79.
- 84 Johansen KL, Smith MW, Unruh ML, Siroka AM, O'Connor TZ, Palevsky PM, and the VA/NIH Acute Renal Failure Trial Network. Predictors of health utility among 60-day survivors of acute kidney injury in the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network Study. *Clin J Am Soc Nephrol* 2010; **5**: 1366–72.
- 85 Joyce VR, Smith MW, Johansen KL, et al, and the Veteran Affairs/National Institutes of Health Acute Renal Failure Trial Network. Health-related quality of life as a predictor of mortality among survivors of AKI. *Clin J Am Soc Nephrol* 2012; **7**: 1063–70.
- 86 Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012; **81**: 442–48.
- 87 Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int* 2012; **81**: 477–85.
- 88 Jones J, Holmen J, De Graauw J, Jovanovich A, Thornton S, Chonchol M. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. *Am J Kidney Dis* 2012; **60**: 402–08.
- 89 Butani L, Morgenstern BZ. Long-term outcome in children after Henoch-Schönlein purpura nephritis. *Clin Pediatr (Phila)* 2007; **46**: 505–11.
- 90 Garg AX, Suri RS, Barrowman N, et al. Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: a systematic review, meta-analysis, and meta-regression. *JAMA* 2003; **290**: 1360–70.
- 91 Mammen C, Al Abbas A, Skippen P, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. *Am J Kidney Dis* 2012; **59**: 523–30.
- 92 Siew ED, Peterson JF, Eden SK, et al. Outpatient Nephrology Referral Rates after Acute Kidney Injury. *J Am Soc Nephrol* 2011; **23**: 305–12.
- 93 Morsch C, Thomé FS, Balbinotto A, Guimarães JF, Barros EG. Health-related quality of life and dialysis dependence in critically ill patient survivors of acute kidney injury. *Ren Fail* 2011; **33**: 949–56.
- 94 Macedo E, Zanetta DM, Abdulkader RC. Long-term follow-up of patients after acute kidney injury: patterns of renal functional recovery. *PLoS One* 2012; **7**: e36388.
- 95 Sinha R, Nandi M, Tullus K, Marks SD, Taraphder A. Ten-year follow-up of children after acute renal failure from a developing country. *Nephrol Dial Transplant* 2009; **24**: 829–33.
- 96 Fischer MJ, Brimhall BB, Lezotte DC, Glazner JE, Parikh CR. Uncomplicated acute renal failure and hospital resource utilization: a retrospective multicenter analysis. *Am J Kidney Dis* 2005; **46**: 1049–57.
- 97 Dasta JF, Kane-Gill SL, Durtschi AJ, Pathak DS, Kellum JA. Costs and outcomes of acute kidney injury (AKI) following cardiac surgery. *Nephrol Dial Transplant* 2008; **23**: 1970–74.
- 98 James MT, Tonelli M, and the Alberta Kidney Disease Network. Financial aspects of renal replacement therapy in acute kidney injury. *Semin Dial* 2011; **24**: 215–19.
- 99 Wald R, Quinn RR, Luo J, et al, and the University of Toronto Acute Kidney Injury Research Group. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. *JAMA* 2009; **302**: 1179–85.
- 100 Waikar SS, Winkelmayer WC. Chronic on acute renal failure: long-term implications of severe acute kidney injury. *JAMA* 2009; **302**: 1227–29.
- 101 Caletti MG, Petetta D, Jaitt M, Casaliba S, Gimenez A. Hemolytic uremic syndrome (HUS): medical and social costs of treatment. *Medicina (B Aires)* 2006; **66** (suppl 3): 22–26.



Global Kidney Disease 1

Evolving importance of kidney disease: from subspecialty to global health burden

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Lancet 2013; 382: 158–69

Published Online

May 31, 2013

[http://dx.doi.org/10.1016/](http://dx.doi.org/10.1016/S0140-6736(13)60439-0)

S0140-6736(13)60439-0

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

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In the past decade, kidney disease diagnosed with objective measures of kidney damage and function has been recognised as a major public health burden. The population prevalence of chronic kidney disease exceeds 10%, and is more than 50% in high-risk subpopulations. Independent of age, sex, ethnic group, and comorbidity, strong, graded, and consistent associations exist between clinical prognosis and two hallmarks of chronic kidney disease: reduced glomerular filtration rate and increased urinary albumin excretion. Furthermore, an acute reduction in glomerular filtration rate is a risk factor for adverse clinical outcomes and the development and progression of chronic kidney disease. An increasing amount of evidence suggests that the kidneys are not only target organs of many diseases but also can strikingly aggravate or start systemic pathophysiological processes through their complex functions and effects on body homeostasis. Risk of kidney disease has a notable genetic component, and identified genes have provided new insights into relevant abnormalities in renal structure and function and essential homeostatic processes. Collaboration across general and specialised health-care professionals is needed to fully address the challenge of prevention of acute and chronic kidney disease and improve outcomes.

Introduction

More than 50 years ago, nephrology emerged as a medical subspecialty dealing with the effects of severely impaired kidney function on body homeostasis. At that time, the understanding of renal physiology and the complex and diverse involvement of kidney function on various body functions was ahead of its clinical application. Few options to treat renal disorders of mineral and electrolyte handling existed, hormonal deficiencies resulting from kidney disease could not be corrected, and almost no techniques were available to prolong the life of individuals with kidney failure.

Nephrology progressed gradually with the establishment of renal pathology and a better understanding of disease entities, but the first major change occurred when dialysis and transplantation became widely available in the 1960s. The ability to provide life-sustaining

renal replacement therapy was an outstanding achievement in medicine. Unsurprisingly, nephrologists have since strived to optimise renal replacement therapy and the prevention and treatment of comorbidities in patients with renal failure. However, the costs associated with these achievements are high. In countries that can afford to offer renal replacement therapy to all patients with renal failure, the proportion of health-care expenditure for this group of patients is far out of proportion to its size.^{1,2} In most countries, economic constraints allow only restricted access to this expensive chronic treatment, which creates striking social inequalities and pressure on constrained health-care resources.³

By contrast with the importance and obvious relevance of chronic kidney failure requiring replacement therapy, the effect of less severe chronic kidney disease, which affects far more patients, had for a long time been largely ignored by the medical community, policy makers, and the public. Reduced kidney function was thought to be of little importance until the glomerular filtration rate reached less than 15%. This viewpoint resulted in two sets of terms to distinguish between patients with so-called end-stage renal disease and others with a lesser degree of renal impairment, who were often collectively summarised as pre-end-stage renal disease or pre-dialysis patients. Moreover, numerous vague and poorly defined terms were commonly used (eg, renal insufficiency or pre-uraemia) in parallel to nomenclature

Key messages

- Chronic kidney disease is chiefly defined by a reduction in glomerular filtration rate and increased urinary albumin excretion
- Chronic kidney disease affects more than 10% of the population in many countries worldwide
- Causes of chronic kidney disease are complex and include common diseases such as hypertension, metabolic syndrome, and diabetes, and various less common diseases that mainly affect the kidney
- Chronic kidney disease predisposes to acute kidney injury and vice versa
- Even mild forms of kidney disease are associated with various adverse effects on body functions and an increased risk of mortality and cardiovascular morbidity
- Genetic causes of specific forms of kidney disease and susceptibility to development of kidney disease in the context of other disorders are increasingly recognised
- A multilevel interdisciplinary approach will be needed to address the public health burden of kidney disease

Search strategy and selection criteria

References included in this Series were identified by the authors, based on their respective areas of expertise and supplemented by unsystematic database searches.

describing the cause of kidney disease (eg, glomerulonephritis, polycystic kidney disease, or diabetic nephropathy). However a uniform and unequivocal definition of chronic kidney disease was unavailable.

Only in 2002 did the medical community first agree on a uniform definition and staging system for chronic kidney disease, based on measures of kidney function and independent of the cause of impaired kidney function.^{4,5} Application of this uniform concept to large databases showed that chronic kidney disease is far more frequent than was appreciated previously.⁶ More than 10% of people have chronic kidney disease and the overall prevalence at least equals that of diabetes.⁷ As with many other chronic diseases, the prevalence of chronic kidney disease increases with age, exceeding 20% in individuals older than 60 years and 35% in those older than 70 years.⁸ The importance of chronic kidney disease became apparent when large analyses showed that even early-stage disease is associated with increased prevalence and severity of numerous disorders and adverse outcomes. In particular, chronic kidney disease is now recognised as a very relevant and independent cardiovascular risk factor (see paper 5 in this Series).^{9,10}

Similar considerations hold true for acute changes in kidney function. Acute renal failure was well known to be associated with poor prognosis, but was regarded as harmless and reversible for a long time, provided patients survived the critical condition during which it occurred. However, even small, transient changes in serum creatinine (suggesting temporary decreases in glomerular filtration rate) have been associated with significantly worsened prognosis, including a strikingly increased risk of mortality and development and progression of chronic kidney disease.^{11,12} After several initiatives were undertaken, a uniform definition and staging of what is now known as acute kidney injury was developed, which could potentially further advance the specialty.¹³

These developments, which were not based on technical, surgical, or immunological progress, but rather on a consensus for a uniform terminology and its application with rigorous epidemiological methods, has greatly expanded the focus on kidney disease beyond nephrology. Standardised terminology has stimulated research, affected patient care, and influenced public policies. And, as for any major advancement, it has also raised new questions. The seemingly most straightforward, but most pressing, of these questions are why is kidney disease so frequent and why is it associated with such a poor prognosis? To answer these two questions, researchers might need to return to the physiology of the organ to better understand why the kidney is a frequent target of many chronic disturbances and why, conversely, disorders of kidney function affect extrarenal tissues so strikingly, in particular the cardiovascular system. Aspects of renal function generally accepted to be understood need to be revisited. Additionally, linkage of the new definitions and staging of acute and chronic kidney disease with genomic, proteomic, and

metabolomic information offers new opportunities to understand underlying mechanisms of disease.

Here, we aim to review the central role of the kidney for body homeostasis and its fate as a target organ of disease. We will also describe the current definitions and staging systems for chronic kidney disease and acute kidney injury, and advances in understanding of the genetic predisposition to kidney disease. Subsequent articles in this series will focus on the global effects, clinical consequences, and management of chronic kidney disease¹⁴ and acute kidney injury;¹⁵ the link between kidney disease and cardiovascular disease;¹⁶ the effects of maternal, neonatal, and child health on kidney health;¹⁷ and future perspectives of the specialty.¹⁸

The kidney and body function

Each kidney contains about 1 million functional units, nephrons, consisting of numerous specialised cell types originating from distinct embryological lineages (figure 1). Each nephron contains a filtrating body, the glomerulus, and a long tubule made of a dozen differentiated segments. The final parts of these tubules are interconnected to form the collecting ducts, which open into the renal pelvis.

The basic principles of kidney physiology dictate the central role played by this organ in excretory, metabolic, and endocrine functions. Although the kidneys excrete only about 1.5 L of urine daily, they are perfused with 20% of the cardiac output and form about 180 L of ultrafiltrate every day, which is profoundly modified during tubular passage. This function exposes the kidney to the interior milieu unlike any other organ and at the same time makes the body composition very sensitive to changes in kidney function.

The glomerular filtration barrier consists of the fenestrated endothelial cells, an elaborate basement membrane, and an intricate layer formed by the foot processes of highly differentiated epithelial cells called podocytes.¹⁹ The filtration barrier is permeable to water, small solutes, and low-molecular-weight proteins up to the mass of albumin, but largely precludes the filtration of plasma proteins with a mass of more than 60–70 kDa, especially if they are negatively charged. Thus the glomerular filtration rate, the product of the filtration area, the hydraulic permeability, and the net ultrafiltration pressure, yields a large ultrafiltrate containing plasma solutes and several grams of low-molecular-weight proteins. Any disturbance in glomerular haemodynamics or structure can result in reduced glomerular filtration rate or increased leakage of proteins into the urine—two classic signs of renal disease.

Along the tubular segments of the nephron, the ultrafiltrate undergoes a series of modifications with massive reabsorption of low-molecular-weight proteins, solutes, and water, secretion of a gel-like protein called uromodulin (Tamm-Horsfall protein) and elimination of excess potassium, acids, and bases (figure 1).²⁰

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The processes affecting urine composition are mediated by polarised transport systems operating in the epithelial cells lining the tubules. The proximal tubule reabsorbs the bulk (about two-thirds) of filtered solutes and water. In addition the cells lining these tubules possess multiligand receptors involved in the endocytic uptake of filtered proteins that include hormones, carrier proteins (eg, for vitamins), and enzymes. Once reabsorbed, these proteins are metabolised by proximal tubular cells, as the human urine is virtually devoid of plasma proteins under physiological conditions. This massive uptake of proteins plays an important role in metabolic clearance, hormone homeostasis, and conservation of essential vitamins (vitamin D, vitamin A, and vitamin B12), and provides a protein-free milieu for the cells lining distal nephron segments.²¹ Organic molecules and drug metabolites are secreted into the urine via specific transporters located in the last part of the proximal tubule.

The tubule segments forming the loop of Henle generate the hypertonic environment in the medulla,

necessary for concentrating the urine, and mediate the paracellular reabsorption of Ca^{2+} and Mg^{2+} under the control of the $\text{Ca}^{2+}/\text{Mg}^{2+}$ -sensing receptor.²² Specialised epithelial cells, located at the junction between the thick ascending limb of the loop of Henle and the distal nephron (macula densa) sense the tubular NaCl concentration and interact with renin-containing granular cells in the afferent arterioles to regulate the glomerular blood flow through a mechanism called tubuloglomerular feedback.²³ The distal nephron, which includes the distal convoluted tubule, the connecting tubule, and the collecting ducts, is responsive to aldosterone and vasopressin and regulates the final urine composition and concentration.²⁴ Several tubular transport processes can be targeted by specific drugs, including diuretics, aquaretics, calcimimetics, and the more recently developed inhibitors of glucose reabsorption.²⁵

Excretory, metabolic, and endocrine functions of the kidney mediate essential interactions with several organs, sustaining an array of vital functions (figure 2), including regulation of body water and thirst, blood pressure, ventilation, drug metabolism, potassium balance, erythropoiesis, calcium and phosphate metabolism, and acid-base homeostasis.

The regulation of NaCl excretion, which is crucial for extracellular fluid volume and blood pressure control, is influenced by the renin-angiotensin-aldosterone system, the atrial natriuretic peptide, the sympathetic nervous system and, to a lesser extent, the antidiuretic hormone arginine vasopressin.²⁶ Renal excretion of potassium is mainly dependent on the distal tubular flow rate and the release of aldosterone and its action on the principal cells of the distal nephron. The regulation of body water content (osmoregulation) involves the action of vasopressin on aquaporin-mediated transport of water.^{27,28} The regulation of the phosphorus and calcium balance reflects complex interactions between bone, parathyroid glands, intestine, and tubular segments, involving fibroblast growth factor (FGF) 23, klotho, parathyroid hormone, and vitamin D.^{29,30} The kidney is also a main site of systemic oxygen sensing, regulating the oxygen supply to red blood cells and hence tissue oxygen supply by hypoxia-inducible erythropoietin production in peritubular fibroblasts of the renal cortex.³¹

Apart from control of body homeostasis, the kidney is also involved in immune function. Dendritic cells and macrophages, which form a network in the renal interstitium, contribute to innate and adaptive immunity and are increasingly recognised for their sentinel role against kidney injury and infection and their potential contribution to progression of kidney disease.³² The renal tubule epithelial cells also express Toll-like receptors (TLRs), including TLR4, of the innate immune system and could be involved in triggering an innate immune response to bacterial and viral infections or ischaemic stress.³³

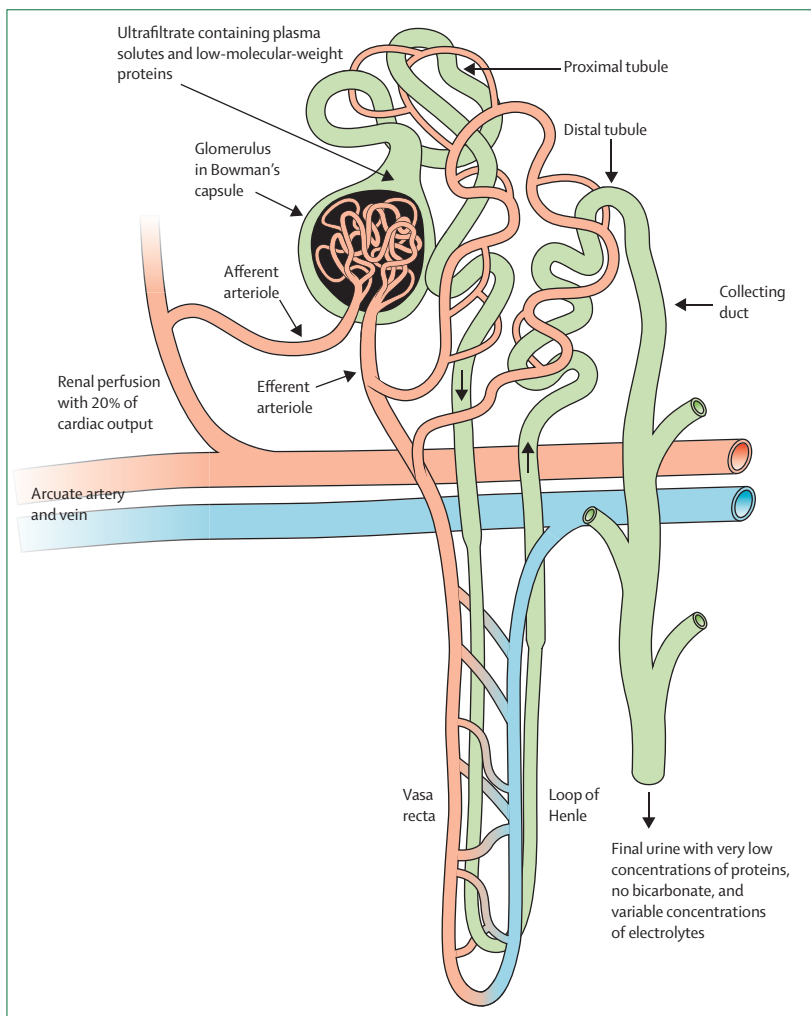


Figure 1: Structure of the nephron

Kidney disease

The present definition and staging of chronic kidney disease and acute kidney injury were proposed by independent guideline development workgroups.^{13,34} The criteria were based on, or were partly validated by, major research efforts that have revolutionised the understanding of outcomes of kidney disease. The foundation for the definition and staging systems is the strong, graded, and consistent association of measures of abnormalities in kidney structure and function with clinical prognosis, independent of age, sex, ethnic group, location, and comorbid conditions.³⁵ The rationale for development of definitions and staging systems based on these measures is the belief that uniform terminology and explicit and objective criteria for assessment enable early identification of kidney disease, recognition of its health effects, including regional and ethnic differences and—most importantly—the development of tailored interventions to improve outcomes.

Chronic kidney disease and acute kidney injury can be detected straightforwardly by the non-nephrologist in clinical practice, and their prevalence and prognosis have been rigorously studied as they relate to public health. However, measurements for assessment of kidney function and structure continue to evolve, the definitions of chronic kidney disease and acute kidney injury are not yet fully harmonised with each other, and evidence for improved outcomes because of the introduction of these definitions is not strong.

Figure 3 shows a conceptual model of the association of kidney disease, irrespective of duration, with adverse outcomes. Kidney disease is defined as a heterogeneous group of disorders affecting kidney structure and function. Even mild abnormalities in measures of structure and function are associated with increased risk of kidney failure or development of complications in other organ systems, especially cardiovascular disease. The clinical presentation and course of the disease are variable. Kidney disease can be defined as acute or chronic, dependent on duration (≤ 3 months vs > 3 months). Acute kidney injury is defined as a subgroup of acute kidney disease in which changes in kidney function occur within 1 week. The association between acute kidney injury and chronic kidney disease is complex: acute kidney injury can lead to chronic kidney disease, and chronic kidney disease increases the risk of acute kidney injury.³⁶

Table 1 summarises the definitions, stages, and burden of chronic kidney disease and acute kidney injury. Both disorders are defined by objective measures of kidney damage (albuminuria, abnormalities in the urine sediment, imaging, or biopsy) and function (decreased glomerular filtration rate, increasing serum creatinine concentrations, or decreased urine output), without reference to the cause of kidney disease. This feature is of particular importance because inclusion of the cause of kidney disease would have precluded the application of the definition in epidemiological studies and in many

clinical scenarios in which the cause was unknown or undocumented. Chronic kidney disease and acute kidney injury are categorised into stages on the basis of the severity in abnormalities in these measures. Clinical practice guidelines for both disorders emphasise a stage-based approach to evaluation and management, complementing the traditional approaches emphasising

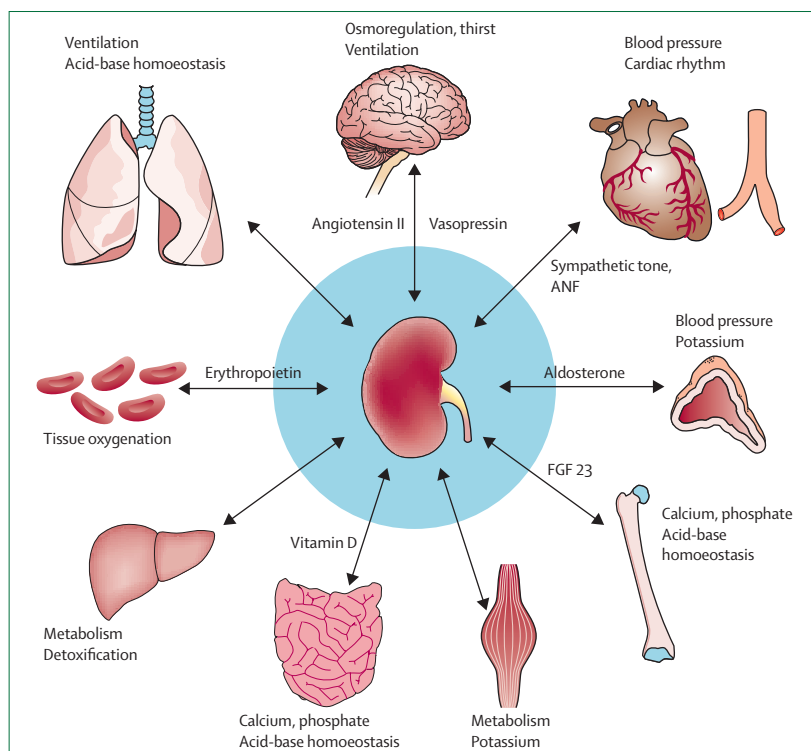


Figure 2: Effect of kidney function on essential homeostatic processes
FGF=fibroblast growth factor. ANF=atrial natriuretic factor.

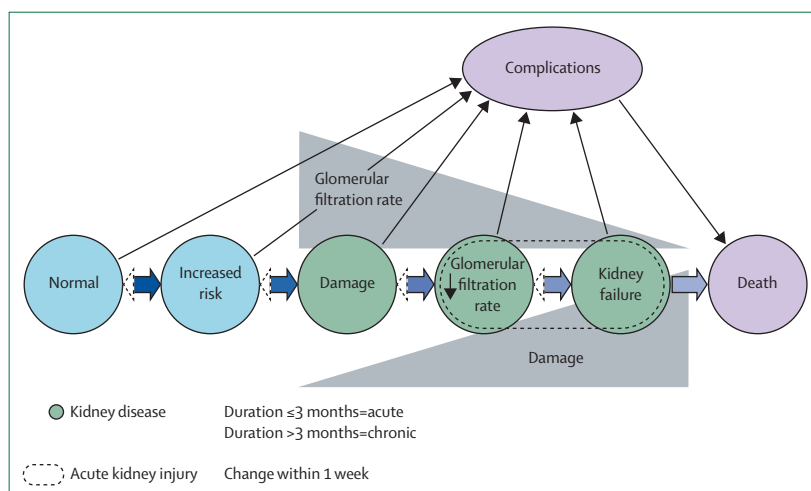


Figure 3: Factors associated with increased risk of kidney disease (blue), stages of disease (green), and complications (including death; purple)
Horizontal arrows show transitions between stages (kidney outcomes). Solid arrows pointing from left to right show progression of kidney disease. Dashed arrowheads pointing from right to left show remission. Grey triangles show continuous nature of changes in glomerular filtration rate and kidney damage.

	Chronic kidney disease	Acute kidney injury
Definition		
Functional criteria	GFR <60 mL/min per 1.73 m ² for >3 months	Increase in serum creatinine by 50% within 7 days; increase in serum creatinine by 26.5 µmol/L (0.3 mg/dL) within 2 days; or oliguria
Structural criteria	Kidney damage for >3 months (albuminuria is the most common marker of kidney damage and is also associated with rapid progression)	None
Staging	GFR categories (mL/min per 1.73 m ²) and related terms†: G1 ≥90 (normal or high); G2 60–89 (mildly decreased‡); G3a 45–59 (mildly to moderately decreased); G3b 30–44 (moderately to severely decreased); G4 15–29 (severely decreased); G5 <15 (kidney failure) Albuminuria categories, approximate equivalent for AER (mg per day) and ACR (mg/g) and related terms: A1 <30 (normal to mildly increased); A2 30–300 (moderately increased‡); A3 >300 (severely increased‡)	Stages based on serum creatinine or urine output; stage 1: serum creatinine ≥1.5–1.9 times baseline, ≥26.5 µmol/L increase, or urine output <0.5 mL/kg per h for 6–12 h; stage 2: serum creatinine ≥2.0–2.9 times baseline or urine output <0.5 mL/kg per h for ≥12 h; stage 3: serum creatinine ≥3.0 times baseline, ≥353.6 µmol/L (≥4 mg/dL), renal replacement therapy, or (in patients <18 years) a decrease in estimated GFR to <35 mL/min per 1.73 m ² , urine output <0.3 mL/kg per h for ≥24 h, or anuria for ≥12 h
Burden*		
Prevalence	~10% of adults (from 4% at 20–39 years to 47% at ≥70 years in the USA) ^{6,8,37,38}	Not applicable for a short-term illness (history of acute kidney injury of any severity present in 45% at chronic kidney disease stage ≥4) ³⁹
Annual incidence	~1% in middle age; twice as frequent in black compared with white populations ^{40–42}	Acute kidney injury requiring hospital admission in Alberta, Canada for patients without chronic kidney disease 0.1% (0.01% requiring dialysis); for patients with stage 3 disease 0.5–7.1% (0.03–0.17%); for patients with stage 4 disease 7.0–11.7% (0.5–2.5%); and 34.8% for acute kidney injury of any severity in chronic kidney disease stage ≥4 ^{39,43} For patients already admitted to hospital, rates are ~10–20% for any acute kidney injury with 0.3% requiring dialysis (highest with sepsis, cancer and surgery)
Lifetime cumulative incidence	~50% for chronic kidney disease ⁴⁴ and ~2% in white and ~7% in black populations for end-stage renal disease ^{45,46}	..

GFR=glomerular filtration rate. AER=albumin excretion rate. ACR=albumin-to-creatinine ratio. *Varies by age and risk factor distribution. †In the absence of evidence of kidney damage, GFR category G1 or G2 do not fulfil the criteria for chronic kidney disease. ‡Terms for categories G2 and A2 are relative to young adult levels; category A3 includes nephrotic syndrome (albumin excretion usually >2200 mg/day [ACR >2220 mg/g]).

Table 1: Definitions, stages, and burden of chronic kidney disease and acute kidney injury

cause of disease.^{4,13,34} The estimates of burden of disease are an approximation made on the basis of a synthesis of available data; substantial variation is noted dependent on the number of risk factors assessed and availability of data in different countries and regions.

The juxtaposition of new definitions and staging systems (based mainly on laboratory measures) and traditional notions (based primarily on causes of disease) has created substantial controversy within the specialty.⁴⁷ Such controversy has been inherently valuable in stimulating research, which has ultimately validated the new concepts and subsequently led to international collaborations and consensus.⁴⁸

Chronic kidney disease

The impetus for the first guidelines defining chronic kidney disease in 2002 stemmed from the rising incidence and prevalence of chronic kidney failure, with associated high cost and poor outcomes, and concerns about late referral to nephrologists.⁴ The recommendations focused on estimation of glomerular filtration rate from serum creatinine and ascertainment of markers of kidney damage (primarily albuminuria). Methodological issues about which measurements to use were a key discussion point. Widespread variation in clinical laboratory procedures for assaying and reporting of serum creatinine concentration drove international initiatives to standardise assays and develop more accurate equations to estimate glomerular filtration rate.^{49,50} Through integrated efforts of the clinical chemistry and nephrology

communities, laboratories are now expected to use standardised methods for creatinine assays and report estimated glomerular filtration rate with validated estimating equations whenever possible.^{51,52} Subsequently, cystatin C was added as a variable to estimate glomerular filtration rate and prognosis, leading to advances in detection and classification of chronic kidney disease.^{53,54} Standardisation and international consensus about urine albumin measurements is an active area of work.⁵⁵ In 2013, the global organisation Kidney Disease: Improving Global Outcomes (KDIGO) published a chronic kidney disease guideline update³⁴ that adds cause of kidney disease and albuminuria stages to the staging system, thus acknowledging the prognostic importance of albuminuria concentrations.^{16,35,48}

Acute kidney injury

KDIGO also developed an acute kidney injury guideline,¹³ recognising that the prognosis of acute kidney failure had not improved in decades, despite substantial improvements in intensive care and methods of dialysis, and that small declines in glomerular filtration rate, which are not severe enough to be classified as acute kidney failure, are associated with adverse outcomes. The acute kidney injury guideline is based on earlier efforts to define the disorder^{56,57} and concentrates on changes in serum creatinine or reduction in urine output as manifestations of direct injury to the kidney and acute impairment of function. Unlike chronic kidney disease, markers of damage are not included in the definition of acute kidney

injury, but there is an intensive investigation of urinary biomarkers that precede the reduction in glomerular filtration rate (eg, kidney injury molecule 1, neutrophil gelatinase-associated lipocalin, and interleukin 18), and might allow early identification and treatment.^{15,58}

Kidney as a cause and target organ of disease

Diseases affecting the kidney are usually categorised into primary and secondary diseases (table 2). However, with increased understanding of the underlying causes of disease, this classification becomes indistinct, because most diseases that mainly manifest in the kidney are associated with extrarenal pathogenesis and systemic manifestations. In view of its notable role in the circulation, the kidney is frequently a target organ of systemic vascular, haemodynamic, metabolic, and inflammatory disorders. Involvement of the kidney in many pathogenic processes originating outside the kidney aggravates disease and impairs prognosis. Although many kidney diseases are rare (and are the centre of specialised nephrological care), increasing evidence suggests an important role of the kidney in highly prevalent, complex disorders, including obesity, diabetes, and hypertension.

Obesity, metabolic syndrome, and diabetes

Prevalence of obesity has increased substantially in the past century. In the USA, obesity (body-mass index >30 kg/m²) has increased in men aged 60 years from 3·4% in 1890 to more than 30% in 2000.⁵⁹ Obesity also presents a serious health threat in developing countries.⁶⁰ The increase in obesity has been accompanied by notable increases in hypertension, diabetes, cardiovascular disease, and chronic kidney disease.^{8,61} The association of chronic kidney disease with an increased frequency of obesity is partly because hypertension and diabetes are known causes of kidney disease and failure. Notably, however, kidney disease begins very early in people who go on to become obese. Thus, in individuals with the metabolic syndrome (a fat storage disorder that affects up to 25% of high-income populations, and is

characterised by truncal obesity in combination with any two of the following factors: increased triglyceride concentrations, low HDL cholesterol, increased blood pressure, increased fasting plasma glucose levels, or previously diagnosed type 2 diabetes), the prevalence of chronic kidney disease increases with the number of traits.⁶² In turn, the presence of chronic kidney disease in patients with metabolic syndrome increases their risk of development of cardiovascular disease. Why individuals with metabolic syndrome develop albuminuria and decreases in glomerular filtration rate before the development of significant hypertension or diabetes is not known. One possibility is that underlying mechanisms might drive both kidney damage and metabolic syndrome, such as endothelial dysfunction and oxidative stress (which are common to both disorders). Diets high in added sugars might have a key role in development of metabolic syndrome and kidney disease, particularly from the ingestion of fructose (present in sucrose and high-fructose corn syrup) that can lead to generation of uric acid.⁶³ Mild kidney disease is induced in rats fed a high fructose diet.⁶⁴ Low-grade systemic inflammation, which is also present in these disorders, might also result in changes in adipokines and other substances that can affect glomerular capillary wall function.⁶⁵

Arterial hypertension

The pathogenesis of hypertension shows that the kidney can have an important role in health and disease even when renal function, defined by glomerular filtration rate, is normal. Primary hypertension, defined as a blood pressure of more than 140/90 mm Hg, was once present in only 5–10% of the adult population in the early 1900s, but has meanwhile increased to a prevalence of 20–40% in most developed countries, and has been projected to affect more than 1·5 billion people worldwide by 2025.⁶⁶ Most studies suggest that the underlying defect involved is a relative inability of the kidney to excrete salt, and this defect can be shown despite a normal or only slightly depressed glomerular filtration rate.^{67,68} A characteristic haemodynamic finding in the kidney is renal

	Examples of primary kidney diseases	Examples of systemic diseases affecting the kidney
Glomerular diseases	Diffuse, focal or crescentic proliferative glomerulonephritis; focal and segmental glomerulosclerosis, membranous nephropathy, and minimal change disease	Obesity, metabolic syndrome and diabetes, systemic autoimmune diseases, systemic infections, drugs, complement diseases, and neoplasias and haemopoietic diseases
Vascular diseases	ANCA-associated renal limited vasculitis, and fibromuscular dysplasia	Hypertension, atherosclerosis, ischaemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, and systemic sclerosis
Tubulointerstitial diseases	Urinary-tract infections, stones, and obstruction	Systemic infections, sarcoidosis, drugs, urate, environmental toxins (eg, lead, aristolochic acid), and neoplasia (myeloma)
Cystic and other congenital diseases	Renal dysplasia, medullary cystic disease, and podocytopathies	Autosomal-dominant polycystic kidney disease, Alport syndrome, and Fabry disease

ANCA=antineutrophil cytoplasmic antibody.

Table 2: Classification of causes of chronic kidney disease based on presence or absence of systemic disease and location within the kidney of pathological-anatomical findings

	Monogenic disease	Complex disease or trait
Inheritance pattern and genetic risk	Mendelian; mutations are necessary and often sufficient for disease manifestation, non-genetic risk factors have few associations	Complex; many genetic factors with weak to moderate effects (relative risk 1.05–1.5) combined with multiple non-genetic risk factors (relative risk 1.5–4.0)
Disease and genetic susceptibility prevalence	Most monogenic diseases are individually rare* (eg, <1 in 40 000 livebirths for recessive and <1 in 1000 for dominant diseases); ADPKD prevalence highest at ~1 per 1000	High for CKD (prevalence ~100 per 1000 adults); common risk allele frequencies (10–50%); much lower for specific chronic kidney disease subtypes such as IgA nephropathy or idiopathic membranous nephropathy
Methods for discovery	Linkage analysis, positional cloning, homozygosity mapping, sequencing (candidate genes or regions, whole exome, or genome)	Association studies (candidate gene, genome-wide arrays) or sequencing, admixture mapping when a large genetic difference between populations is anticipated
Examples	ADPKD, Alport's disease, and UAKD	Population-based chronic kidney disease, estimated glomerular filtration rate, and albuminuria, IgA nephropathy, and idiopathic membranous nephropathy
Cause	ADPKD†: mutations in <i>PKD1</i> or <i>PKD2</i> (currently 929 germline mutations in <i>PKD1</i> and 167 in <i>PKD2</i> classified as likely or definitely pathogenic; Alport's disease: >500 pathogenic mutations in <i>COL4A3</i> – <i>COL4A6</i> ; and UAKD: >50 pathogenic mutations in <i>UMOD</i>	Multifactorial; genetic risk variants for chronic kidney disease or end-stage renal disease: <i>APOL1</i> , <i>UMOD</i> , <i>PRKAG2</i> , <i>AFF3</i> , <i>RGMA/MCTP2</i> , and <i>WDR72</i> ; for estimated glomerular filtration rate: <i>ANXA9/LASS2</i> , <i>GCKR</i> , <i>ALMS1/NAT8</i> , <i>TFDP2</i> , <i>SHROOM3</i> , <i>DAB2</i> , <i>SLC34A1</i> , <i>VEGFA</i> , <i>PRKAG2</i> , <i>PIP5K1B</i> , <i>ATXN2/SH2B3</i> , <i>DACH1</i> , <i>UBE2Q2</i> , <i>UMOD</i> , <i>SLC7A9</i> , <i>SLC47A1</i> , <i>CASP9</i> , <i>CDK12</i> , <i>INO80</i> , <i>DDX1</i> , <i>MPPED2</i> , <i>MHC</i> region, and <i>UNCX</i> ; for albuminuria: <i>CUBN</i> ; for IgA nephropathy: <i>HLA-DRB1/DQA1</i> , <i>PSMB8</i> , <i>HLA-DPA1/DPB2</i> , <i>CFHR3/R1</i> , <i>HORMAD2</i> , <i>TNFSF12/13</i> , <i>DEFA9P-10P</i> , <i>HLA-DQB1/A2</i> , <i>MTMR3</i> , <i>HCG9</i> , and <i>SOX15/MPDU1</i> ; for idiopathic membranous nephropathy: <i>HLA-DQA1</i> and <i>PLA2R1</i>

Genes shown are the gene closest to the SNP with the lowest p value in an associated region, unless functional evidence points towards another nearby gene in the region. Only genome-wide significant findings ($p < 5 \times 10^{-8}$) are reported. CKD, estimated glomerular filtration rate, and albuminuria loci are reported for findings from population-based studies, end-stage-renal disease findings are reported from case-control studies. ADPKD=autosomal-dominant polycystic kidney disease. UAKD=uromodulin-associated kidney disorders. *Affecting fewer than five per 10 000 population. †For the ADPKD mutation database see <http://pkdb.mayo.edu>.

Table 3: Monogenic and complex kidney diseases

vasoconstriction, especially of the preglomerular arteriolar vasculature. Genetic factors affect the ability of the kidney to excrete salt⁶⁹ and determine the risk of development of primary hypertension⁷⁰ and hypertensive kidney disease.^{69,70} Intrauterine factors, known as fetal programming, are also important. In particular, intrauterine malnutrition can be associated with impaired fetal development, resulting in infants with a low birthweight who have a reduced number of nephrons in their kidney and are predisposed to the development of hypertension.⁷¹ Hypertension can also be caused by subtle acquired injury to the kidney, resulting in microvascular damage, peritubular capillary loss, and the infiltration of T cells and macrophages.⁷² The inflammatory infiltrate enhances local oxidative stress and intrarenal angiotensin activity, amplifying the renal vasoconstriction and impairing the excretion of salt. T cells reacting to specific antigens in the kidney, possibly induced by local ischaemia, might contribute to the hypertensive response,⁷³ thus suggesting an autoimmune component of primary hypertension. These mechanisms might also explain how factors associated with the metabolic syndrome, such as endothelial dysfunction, sympathetic nervous overactivity, and hyperuricaemia can induce hypertension, thus providing an important link for the common coexistence of obesity and hypertension.

Genetic predisposition to kidney disease

Clustering of kidney disease in families is well established, but underappreciated. From the 1980s, linkage analysis and subsequently positional cloning emerged as a technique that allowed for the detection of disease-causing mutations in one gene (termed monogenic or Mendelian diseases). In 2010, more than 110 genes underlying monogenic diseases with a renal phenotype

had been described.⁷⁴ The most prominent example is autosomal-dominant polycystic kidney disease (table 3). Although this disease, which is the most frequent monogenic renal disorder usually manifests during adulthood, many other rare monogenic renal diseases have an early and severe onset. With the advent of whole-exome and whole-genome sequencing, the number of identified single-gene defects causing renal disease in affected families is expected to increase rapidly.^{75,76} Such studies will also allow researchers to investigate the combined effect of rare mutations and common disease susceptibility variants, which might help explain some of the high phenotype heterogeneity reported for many monogenic kidney diseases. Overall monogenic diseases are the presumed cause of kidney failure in more than 10% of patients undergoing dialysis, with autosomal-dominant polycystic kidney disease accounting for about 7% of all failures.⁷⁷

Susceptibility to complex multifactorial diseases such as chronic kidney disease is influenced by variation in many genes and non-genetic components. Since 2005, unbiased genome-wide mapping approaches such as admixture linkage disequilibrium and genome-wide association studies have emerged as methods to search for complex kidney disease susceptibility variants (table 3). These studies have identified genomic regions associated with intermediate traits such as estimated glomerular filtration rate,^{78,79} albuminuria,⁸⁰ and chronic kidney disease when applying the aforementioned definition of chronic kidney disease in the general population.⁷⁹ Moreover, genomic regions have been identified that are associated with more specific disease entities such as non-diabetic end-stage renal disease, focal-segmental glomerulosclerosis,^{81–83} immunoglobulin A nephropathy,⁸⁴ and idiopathic membranous nephropathy.⁸⁵

As for other complex diseases, identified genetic risk variants usually only confer small increases in disease risk, with identification requiring large study populations. Common risk variants in the *MYH9/APOL1* region that increase the risk of kidney disease in black populations are an impressive exception because the associated relative risks are very large (fivefold to 17-fold for focal-segmental glomerulosclerosis, threefold in case-control studies of non-diabetic end-stage renal disease, and 29-fold for HIV-associated nephropathy) and the population attributable risk amounts to 70%.^{81,82,86} These risk alleles also contribute to the risk of diabetic kidney disease but the associated risk is smaller, suggesting that non-genetic factors have a larger role than do genetic ones.⁸⁷ The African American Study of Kidney Disease and Hypertension⁸⁸ provided convincing evidence that progressive kidney disease that was labelled hypertensive nephrosclerosis on clinical grounds could be attributed to risk variants in the *APOL1* region, explaining why blood-pressure lowering often failed to halt disease progression in this population. The precise roles of *MYH9/APOL1* in predisposition to kidney disease remain to be identified, but apolipoprotein L1 confers protection against trypanosomiasis, which might have provided a survival advantage in Africans and thereby explains why this group is particularly at risk of focal-segmental glomerulosclerosis and non-diabetic chronic kidney disease.⁸³

The notion that a continuum of genetic risk variants from small to large effects results in different degrees of disease severity is compelling. Rare mutations in *UMOD*—which codes for uromodulin, a protein secreted in large amounts into the urine in the thick ascending limb of loop of Henle—cause monogenic kidney disease,⁸⁹ whereas common *UMOD* variants increase chronic kidney disease susceptibility in the general population.^{90,91} Thus, disorders in uromodulin secretion are of widespread pathophysiological relevance. Other rare inherited diseases that have provided key insights into common disorders of kidney function include monogenic disorders affecting renal handling of NaCl, which improved our understanding of blood pressure regulation and mechanisms of action of diuretics;^{92,93} inherited disorders involving the proximal tubule such as renal Fanconi syndrome, which evidenced the role of receptor-mediated endocytosis in acquired proximal tubule dysfunction and renal disease progression;⁹⁴ and the discovery that several genes causing cystic kidney diseases code for proteins that are located in the primary cilium, which enlarged the scope of these disorders and provided essential information about their multisystemic nature.⁹⁵

Improved understanding of genetic causes of kidney disease has already started to inform treatment decisions. Identification of a genetic cause affecting the glomerular filtration barrier can help avoid ineffective exposure to steroid treatment in children with nephrotic

syndrome.⁹⁶ Genotyping for atypical haemolytic uraemic syndrome can enable prediction of the risk for relapse after renal transplantation.⁹⁷ The clinical relevance of genotyping in patients with kidney disease will probably increase rapidly in the near future. However, genetic insights into complex kidney diseases have not yet proved useful in terms of prediction of chronic kidney disease in the general population.⁹⁸

Complications of kidney disease

In general, all acute and chronic diseases have a worse prognosis in the presence of kidney disease. This association is of particular relevance for the various types of cardiovascular disease,⁹ including acute myocardial infarction,⁹⁹ stroke,¹⁰⁰ and heart failure.¹⁰¹ Chronic kidney disease also worsens the prognosis of patients with metabolic disease and diabetes, chronic pulmonary disease, pneumonia,^{102,103} and other acute infections. An increased incidence of cancer in patients with chronic kidney disease has also been reported, but seems to be linked to increased prevalence of liver cancer and urological cancer in these patients¹⁰⁴ rather than a general increase in cancer risk.

Reasons for the consistent association of kidney disease with poor outcomes are only partly understood. For patients whose kidney disease is a result of systemic disease processes leading to target organ damage at different sites, the severity of kidney disease might show the severity of the systemic, damage-causing process. In addition, direct links exist between kidney function and the damage of extrarenal tissues. Acute kidney injury, for example, induces inflammation and aggravates the response to injury in the lung and other organs.^{105,106} The term cardiorenal syndrome has been coined to describe the complex interaction between impaired cardiac function and kidney disease, to which not only impaired renal salt and water handling but also enhanced renal sympathetic activity contribute.¹⁰⁷ Mechanisms through which kidney disease accelerates atherosclerosis and enhances vascular calcifications also warrant attention, with impaired renal phosphate-handling presumably playing a dominant role.¹⁰⁸ Not only is vascular disease advanced in patients with chronic kidney disease, but several other characteristics of kidney disease might also be regarded as advanced ageing, possibly related to reduced renal expression of the anti-ageing proteohormone klotho.²⁹

Presence of kidney disease also affects management strategies and is associated with a reduced implementation of best practice, presumably because of uncertainties about the risk-benefit balance of diagnostic procedures and therapeutic interventions. Thus, restrictions in the use of imaging procedures that require the application of radiocontrast agents or gadolinium can lead to underdiagnosis in patients with kidney disease. Another potential source of impaired prognosis is error or uncertainty in drug dosing, including drug toxicity

and underdosing. Therapeutic nihilism is especially obvious in the management of acute myocardial infarction in patients with chronic kidney disease, who receive fewer acute coronary interventions and reduced prescription of standard drugs, despite being at increased risk of adverse outcomes of myocardial ischaemia.^{109,110}

Implications for general practice

In view of the importance of kidney function on body homeostasis and the high prevalence of kidney disease, its recognition is important to all providers of health care. Serum creatinine concentrations and urinary excretion of albumin related to creatinine in spot urine samples are straightforward and robust techniques to exclude or diagnose and stage chronic kidney disease.^{4,34} Although the quantitative association between serum creatinine concentrations and glomerular filtration rate is confounded by muscle mass, different formulas have been developed to correct for this influence and to estimate glomerular filtration rate from one-off creatinine readings.³⁴ Use of these formulas in clinical chemistry laboratories allows automatic reporting of estimated glomerular filtration rate and thereby aids detection of kidney disease by the treating physician. Although screening for chronic kidney disease in the general population has not been shown to be cost-efficient, screening is recommended in high-risk groups, such as people with diabetes, hypertension, or a family burden of disease.¹¹¹

Treatment strategies for chronic kidney disease are diverse and depend on the underlying disease and severity of impaired kidney function, complications, and comorbidities. However, blood-pressure control is a mainstay of secondary prevention for most patients. Inhibitors of the renin-angiotensin system (angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers) retard kidney disease progression beyond their blood-pressure-lowering effects, presumably because of their influence on glomerular haemodynamics with a reduction in filtration pressure.¹¹² Attempts to further reduce kidney disease progression and cardiovascular complications through dual blockade of the renin-angiotensin system, however, have failed.^{113,114} Irrespective of specific interventions, the recognition of patients with chronic kidney disease and acute kidney injury as individuals with high risk in all health-care settings is of utmost importance.

Future challenges

Despite the compelling evidence for strong associations of kidney disease with adverse outcomes and increasing insight into possible mechanisms, the ultimate proof for a causal association between impaired kidney function and poor health will rely on proof of benefit after improvements in kidney function. Unfortunately, therapeutic strategies that would enable such a hypothesis to be addressed, are very limited. The number of

randomised clinical trials in nephrology continues to lag behind most other medical specialties.¹¹⁵ In the context of clinical trials, kidney disease is usually an exclusion criterion and very rarely a therapeutic target.

Because of the diverse mechanisms that can affect kidney function and the heterogeneity of natural courses of the disease, therapeutic interventions will probably not be effective unless they are tailored to specific subgroups or stages of kidney disease. Thus, although a unifying perspective has proven crucial, the challenge of the future will be to subdivide the syndromes of chronic kidney disease and acute kidney injury into distinct entities defined by similar pathogenesis, disease states, and complications. New biomarkers will be needed that predict the risk of kidney disease in unaffected individuals and causes, pathomechanisms, and outcomes (renal and non-renal) in individuals with the disease. Integration of multilevel information, including genetics, pathological changes, biomarkers, clinical course, and drug response could eventually result in advanced versions of the present staging systems and form the basis for personalised therapies. The recent discovery of phospholipase A2 as the main glomerular antigen causing membranous nephropathy, the most frequent cause of the nephrotic syndrome in adults,¹¹⁶ the recognition of a specific genetic predisposition for this disease,⁸⁵ the demonstration of increased antigen expression in glomeruli of affected individuals,¹¹⁷ and the assessment of phospholipase A2 antibody titres as diagnostic techniques and indicators of disease activity provides an impressive example for such an integrative approach.¹¹⁸ Apart from studies in single-disease entities, the establishment and prospective assessment of large cohorts of carefully characterised patients with chronic kidney disease will probably have an important role in unravelling distinct categories of kidney disease.^{119,120} If such approaches continue to be successful, the next major breakthrough in renal medicine will hopefully lead to effective halting of kidney disease and its adverse outcomes through specific interventions, and ultimately regeneration of kidney function.¹²¹

Contributors

All authors discussed the overall concept, contributed to specific sections, and reviewed and approved the final version. K-UE prepared the first outline and integrated and edited contributions from all coauthors.

Conflicts of interest

We declare that we have no conflicts of interest.

References

- 1 Kerr M, Bray B, Medcalf J, O'Donoghue DJ, Matthews B. Estimating the financial cost of chronic kidney disease to the NHS in England. *Nephrol Dial Transplant* 2012; **27** (suppl 3): iii73–80.
- 2 Vanholder R, Davenport A, Hannedouche T, et al, and the Dialysis Advisory Group of American Society of Nephrology. Reimbursement of dialysis: a comparison of seven countries. *J Am Soc Nephrol* 2012; **23**: 1291–98.
- 3 Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int* 2011; **80**: 1258–70.
- 4 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39** (suppl 1): S1–266.

- 5 Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; **67**: 2089–100.
- 6 Levey AS, Coresh J. Chronic kidney disease. *Lancet* 2012; **379**: 165–80.
- 7 James MT, Hemmelgarn BR, Tonelli M. Early recognition and prevention of chronic kidney disease. *Lancet* 2010; **375**: 1296–309.
- 8 Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2038–47.
- 9 Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2011; **80**: 572–86.
- 10 Sarnak MJ, Levey AS, Schoolwerth AC, et al, and the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003; **108**: 2154–69.
- 11 Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet* 2012; **380**: 756–66.
- 12 Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012; **81**: 442–48.
- 13 KDIGO. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; **2**: 1–138.
- 14 Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; published online May 31. [http://dx.doi.org/10.1016/S0140-6736\(13\)60687-X](http://dx.doi.org/10.1016/S0140-6736(13)60687-X).
- 15 Lameire NH, Bagga A, Cruz D, et al. Acute kidney injury: an increasing global concern. *Lancet* 2013; published online May 31. [http://dx.doi.org/10.1016/S0140-6736\(13\)60647-9](http://dx.doi.org/10.1016/S0140-6736(13)60647-9).
- 16 Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013; published online May 31. [http://dx.doi.org/10.1016/S0140-6736\(13\)60595-4](http://dx.doi.org/10.1016/S0140-6736(13)60595-4).
- 17 Luyckx VA, Bertram JF, Brenner BM, et al. Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease. *Lancet* 2013; published online May 31. [http://dx.doi.org/10.1016/S0140-6736\(13\)60311-6](http://dx.doi.org/10.1016/S0140-6736(13)60311-6).
- 18 Remuzzi G, Benigni A, Finkelstein FO, et al. Kidney failure: aims for the next 10 years and barriers to success. *Lancet* 2013; published online May 31. [http://dx.doi.org/10.1016/S0140-6736\(13\)60438-9](http://dx.doi.org/10.1016/S0140-6736(13)60438-9).
- 19 Haraldsson B, Nyström J, Deen WM. Properties of the glomerular barrier and mechanisms of proteinuria. *Physiol Rev* 2008; **88**: 451–87.
- 20 Brown D, Bouley R, Păunescu TG, Breton S, Lu HA. New insights into the dynamic regulation of water and acid-base balance by renal epithelial cells. *Am J Physiol Cell Physiol* 2012; **302**: C1421–33.
- 21 Christensen EI, Verroust PJ, Nielsen R. Receptor-mediated endocytosis in renal proximal tubule. *Pflügers Arch* 2009; **458**: 1039–48.
- 22 Ferré S, Hoenderop JG, Bindels RJ. Sensing mechanisms involved in Ca²⁺ and Mg²⁺ homeostasis. *Kidney Int* 2012; **82**: 1157–66.
- 23 Singh P, Thomson SC. Renal homeostasis and tubuloglomerular feedback. *Curr Opin Nephrol Hypertens* 2010; **19**: 59–64.
- 24 Reilly RF, Ellison DH. Mammalian distal tubule: physiology, pathophysiology, and molecular anatomy. *Physiol Rev* 2000; **80**: 277–313.
- 25 Shah NK, Deeb WE, Choksi R, Epstein BJ. Dapagliflozin: a novel sodium-glucose cotransporter type 2 inhibitor for the treatment of type 2 diabetes mellitus. *Pharmacotherapy* 2012; **32**: 80–94.
- 26 Stockand JD. Vasopressin regulation of renal sodium excretion. *Kidney Int* 2010; **78**: 849–56.
- 27 Schrier RW. Vasopressin and aquaporin 2 in clinical disorders of water homeostasis. *Semin Nephrol* 2008; **28**: 289–96.
- 28 Bourque CW. Central mechanisms of osmosensation and systemic osmoregulation. *Nat Rev Neurosci* 2008; **9**: 519–31.
- 29 Kuro-O M. Klotho in health and disease. *Curr Opin Nephrol Hypertens* 2012; **21**: 362–68.
- 30 Martin A, David V, Quarles LD. Regulation and function of the FGF23/klotho endocrine pathways. *Physiol Rev* 2012; **92**: 131–55.
- 31 Gleadle JM. Review article: how cells sense oxygen: lessons from and for the kidney. *Nephrology (Carlton)* 2009; **14**: 86–93.
- 32 Teteris SA, Engel DR, Kurts C. Homeostatic and pathogenic role of renal dendritic cells. *Kidney Int* 2011; **80**: 139–45.
- 33 Smith KD. Toll-like receptors in kidney disease. *Curr Opin Nephrol Hypertens* 2009; **18**: 189–96.
- 34 KDIGO. KDIGO clinical practice guideline for chronic kidney disease. *Kidney Int Suppl* 2013; **3**: 1–150.
- 35 Matsushita K, van der Velde M, Astor BC, et al, and the Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; **375**: 2073–81.
- 36 Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney Int* 2012; **82**: 516–24.
- 37 Matsushita K, Mahmoodi BK, Woodward M, et al, and the Chronic Kidney Disease Prognosis Consortium. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA* 2012; **307**: 1941–51.
- 38 Hallan SI, Matsushita K, Sang Y, et al, for the Chronic Kidney Disease Prognosis Consortium. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA* 2012; **308**: 3349–60.
- 39 Lafrance JP, Djurdjev O, Levin A. Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort. *Nephrol Dial Transplant* 2010; **25**: 2203–09.
- 40 Bash LD, Coresh J, Köttgen A, et al. Defining incident chronic kidney disease in the research setting: The ARIC Study. *Am J Epidemiol* 2009; **170**: 414–24.
- 41 Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. *JAMA* 2004; **291**: 844–50.
- 42 Peralta CA, Katz R, DeBoer I, et al. Racial and ethnic differences in kidney function decline among persons without chronic kidney disease. *J Am Soc Nephrol* 2011; **22**: 1327–34.
- 43 James MT, Hemmelgarn BR, Wiebe N, et al, for the Alberta Kidney Disease Network. Glomerular filtration rate, proteinuria, and the incidence and consequences of acute kidney injury: a cohort study. *Lancet* 2010; **376**: 2096–103.
- 44 Hoerger TJ, Wittenborn JS, Segel JE, et al, and the Centers for Disease Control and Prevention CKD Initiative. A health policy model of CKD: 1. Model construction, assumptions, and validation of health consequences. *Am J Kidney Dis* 2010; **55**: 452–62.
- 45 Turin TC, Tonelli M, Manns BJ, et al. Lifetime risk of ESRD. *J Am Soc Nephrol* 2012; **23**: 1569–78.
- 46 Kiberd BA, Clase CM. Cumulative risk for developing end-stage renal disease in the US population. *J Am Soc Nephrol* 2002; **13**: 1635–44.
- 47 Eckardt KU, Berns JS, Rocco MV, Kasiske BL. Definition and classification of CKD: the debate should be about patient prognosis—a position statement from KDOQI and KDIGO. *Am J Kidney Dis* 2009; **53**: 915–20.
- 48 Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2011; **80**: 17–28.
- 49 Levey AS, Coresh J, Greene T, et al, and the Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**: 247–54.
- 50 Levey AS, Stevens LA, Schmid CH, et al, and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–12.
- 51 Myers GL, Miller WG, Coresh J, et al, and the National Kidney Disease Education Program Laboratory Working Group. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem* 2006; **52**: 5–18.
- 52 Miller WG. Estimating glomerular filtration rate. *Clin Chem Lab Med* 2009; **47**: 1017–19.
- 53 Inker LA, Schmid CH, Tighiouart H, et al, and the CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; **367**: 20–29.

- 54 Peralta CA, Shlipak MG, Judd S, et al. Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. *JAMA* 2011; **305**: 1545–52.
- 55 Miller WG, Bruns DE, Hortin GL, et al, and the National Kidney Disease Education Program-IFCC Working Group on Standardization of Albumin in Urine. Current issues in measurement and reporting of urinary albumin excretion. *Clin Chem* 2009; **55**: 24–38.
- 56 Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, and the Acute Dialysis Quality Initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; **8**: R204–12.
- 57 Mehta RL, Kellum JA, Shah SV, et al, and the Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**: R31.
- 58 Chawla LS, Kellum JA. Acute kidney injury in 2011: biomarkers are transforming our understanding of AKI. *Nat Rev Nephrol* 2012; **8**: 68–70.
- 59 Helmschen LA, Henderson RM. Changes in the distribution of body mass index of white US men, 1890–2000. *Ann Hum Biol* 2004; **31**: 174–81.
- 60 Dinsa GD, Goryakin Y, Fumagalli E, Suhrcke M. Obesity and socioeconomic status in developing countries: a systematic review. *Obes Rev* 2012; **13**: 1067–79.
- 61 United States Renal Data System. Atlas of end-stage renal disease in the United States. National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Annual Data Report, 2004.
- 62 Chen J, Muntner P, Hamm LL, et al. The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 2004; **140**: 167–74.
- 63 Johnson RJ, Sanchez-Lozada LG, Nakagawa T. The effect of fructose on renal biology and disease. *J Am Soc Nephrol* 2010; **21**: 2036–39.
- 64 Nakayama T, Kosugi T, Gersch M, et al. Dietary fructose causes tubulointerstitial injury in the normal rat kidney. *Am J Physiol Renal Physiol* 2010; **298**: F712–20.
- 65 Sharma K, Ramachandrarao S, Qiu G, et al. Adiponectin regulates albuminuria and podocyte function in mice. *J Clin Invest* 2008; **118**: 1645–56.
- 66 Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; **365**: 217–23.
- 67 Guyton AC, Coleman TG, Cowley AV Jr, Scheel KW, Manning RD Jr, Norman RA Jr. Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. *Am J Med* 1972; **52**: 584–94.
- 68 Wade HM, Textor SC. The role of the kidney in regulating arterial blood pressure. *Nat Rev Nephrol* 2012; **8**: 602–09.
- 69 Lifton RP. Genetic dissection of human blood pressure variation: common pathways from rare phenotypes. *Harvey Lect* 2004–2005; **100**: 71–101.
- 70 Carmelli D, Robinette D, Fabsitz R. Concordance, discordance and prevalence of hypertension in World War II male veteran twins. *J Hypertens* 1994; **12**: 323–28.
- 71 Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. *N Engl J Med* 2003; **348**: 101–08.
- 72 Rodriguez-Iturbe B, Johnson RJ. The role of renal microvascular disease and interstitial inflammation in salt-sensitive hypertension. *Hypertens Res* 2010; **33**: 975–80.
- 73 Guzik TJ, Hoch NE, Brown KA, et al. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med* 2007; **204**: 2449–60.
- 74 Hildebrandt F. Genetic kidney diseases. *Lancet* 2010; **375**: 1287–95.
- 75 Otto EA, Hurd TW, Airik R, et al. Candidate exome capture identifies mutation of SDCCAG8 as the cause of a retinal-renal ciliopathy. *Nat Genet* 2010; **42**: 840–50.
- 76 Chaki M, Airik R, Ghosh AK, et al. Exome capture reveals ZNF423 and CEP164 mutations, linking renal ciliopathies to DNA damage response signaling. *Cell* 2012; **150**: 533–48.
- 77 Devuyst O, Antignac C, Bindels RJ, et al. The ERA-EDTA Working Group on inherited kidney disorders. *Nephrol Dial Transplant* 2012; **27**: 67–69.
- 78 Chambers JC, Zhang W, Lord GM, et al. Genetic loci influencing kidney function and chronic kidney disease. *Nat Genet* 2010; **42**: 373–75.
- 79 Köttgen A, Pattaro C, Böger CA, et al. New loci associated with kidney function and chronic kidney disease. *Nat Genet* 2010; **42**: 376–84.
- 80 Böger CA, Chen MH, Tin A, et al, and the CKDGen Consortium. CUBN is a gene locus for albuminuria. *J Am Soc Nephrol* 2011; **22**: 555–70.
- 81 Kao WH, Klag MJ, Meoni LA, et al, and the Family Investigation of Nephropathy and Diabetes Research Group. MYH9 is associated with nondiabetic end-stage renal disease in African Americans. *Nat Genet* 2008; **40**: 1185–92.
- 82 Kopp JB, Smith MW, Nelson GW, et al. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. *Nat Genet* 2008; **40**: 1175–84.
- 83 Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; **329**: 841–45.
- 84 Gharavi AG, Kiryluk K, Choi M, et al. Genome-wide association study identifies susceptibility loci for IgA nephropathy. *Nat Genet* 2011; **43**: 321–27.
- 85 Stancu HC, Arcos-Burgos M, Medlar A, et al. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. *N Engl J Med* 2011; **364**: 616–26.
- 86 Kopp JB, Nelson GW, Sampath K, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol* 2011; **22**: 2129–37.
- 87 Krop JS, Coresh J, Chambless LE, et al. A community-based study of explanatory factors for the excess risk for early renal function decline in blacks vs whites with diabetes: the Atherosclerosis Risk in Communities study. *Arch Intern Med* 1999; **159**: 1777–83.
- 88 Lipkowitz MS, Freedman BI, Langefeld CD, et al, and the SK Investigators. Apolipoprotein L1 gene variants associate with hypertension-attributed nephropathy and the rate of kidney function decline in African Americans. *Kidney Int* 2013; **83**: 114–20.
- 89 Hart TC, Gorro MC, Hart PS, et al. Mutations of the UMOD gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. *J Med Genet* 2002; **39**: 882–92.
- 90 Köttgen A, Glazer NL, Dehghan A, et al. Multiple loci associated with indices of renal function and chronic kidney disease. *Nat Genet* 2009; **41**: 712–17.
- 91 Rampoldi L, Scolari F, Amoroso A, Ghiggeri G, Devuyst O. The rediscovery of uromodulin (Tamm-Horsfall protein): from tubulointerstitial nephropathy to chronic kidney disease. *Kidney Int* 2011; **80**: 338–47.
- 92 Ji W, Foo JN, O'Roak BJ, et al. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* 2008; **40**: 592–99.
- 93 Devuyst O. Salt wasting and blood pressure. *Nat Genet* 2008; **40**: 495–96.
- 94 Devuyst O, Thakker RV. Dent's disease. *Orphanet J Rare Dis* 2010; **5**: 28.
- 95 Hildebrandt F, Benzing T, Katsanis N. Ciliopathies. *N Engl J Med* 2011; **364**: 1533–43.
- 96 Santin S, Bullich G, Tazón-Vega B, et al. Clinical utility of genetic testing in children and adults with steroid-resistant nephrotic syndrome. *Clin J Am Soc Nephrol* 2011; **6**: 1139–48.
- 97 Noris M, Remuzzi G. Genetics and genetic testing in hemolytic uremic syndrome/thrombotic thrombocytopenic purpura. *Semin Nephrol* 2010; **30**: 395–408.
- 98 O'Seaghdha CM, Yang Q, Wu H, Hwang SJ, Fox CS. Performance of a genetic risk score for CKD stage 3 in the general population. *Am J Kidney Dis* 2012; **59**: 19–24.
- 99 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296–305.
- 100 Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ* 2010; **341**: c4249.

- 101 Bagshaw SM, Cruz DN, Aspromonte N, et al. Epidemiology of cardio-renal syndromes: workgroup statements from the 7th ADQI Consensus Conference. *NDT* 2010; **25**: 1406–16.
- 102 Viasus D, Garcia-Vidal C, Cruzado JM, et al. Epidemiology, clinical features and outcomes of pneumonia in patients with chronic kidney disease. *Nephrol Dial Transplant* 2011; **26**: 2899–906.
- 103 James MT, Quan H, Tonelli M, et al, and the Alberta Kidney Disease Network. CKD and risk of hospitalization and death with pneumonia. *Am J Kidney Dis* 2009; **54**: 24–32.
- 104 Weng PH, Hung KY, Huang HL, Chen JH, Sung PK, Huang KC. Cancer-specific mortality in chronic kidney disease: longitudinal follow-up of a large cohort. *Clin J Am Soc Nephrol* 2011; **6**: 1121–28.
- 105 Lie ML, White LE, Santora RJ, Park JM, Rabb H, Hassoun HT. Lung T lymphocyte trafficking and activation during ischemic acute kidney injury. *J Immunol* 2012; **189**: 2843–51.
- 106 Ahuja N, Andres-Hernando A, Altmann C, et al. Circulating IL-6 mediates lung injury via CXCL1 production after acute kidney injury in mice. *Am J Physiol Renal Physiol* 2012; **303**: F864–72.
- 107 Ronco C, McCullough P, Anker SD, et al, and the Acute Dialysis Quality Initiative (ADQI) consensus group. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J* 2010; **31**: 703–11.
- 108 Toussaint ND, Pedagogos E, Tan SJ, et al. Phosphate in early chronic kidney disease: associations with clinical outcomes and a target to reduce cardiovascular risk. *Nephrology (Carlton)* 2012; **17**: 433–44.
- 109 Charytan DM, Setoguchi S, Solomon DH, Avorn J, Winkelmayer WC. Clinical presentation of myocardial infarction contributes to lower use of coronary angiography in patients with chronic kidney disease. *Kidney Int* 2007; **71**: 938–45.
- 110 Winkelmayer WC, Charytan DM, Brookhart MA, Levin R, Solomon DH, Avorn J. Kidney function and use of recommended medications after myocardial infarction in elderly patients. *Clin J Am Soc Nephrol* 2006; **1**: 796–801.
- 111 Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 2007; **72**: 247–59.
- 112 Turner JM, Bauer C, Abramowitz MK, Melamed ML, Hostetter TH. Treatment of chronic kidney disease. *Kidney Int* 2012; **81**: 351–62.
- 113 Mann JF, Schmieder RE, McQueen M, et al, and the ONTARGET investigators. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 2008; **372**: 547–53.
- 114 Parving HH, Brenner BM, McMurray JJ, et al, and the ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012; **367**: 2204–13.
- 115 Palmer SC, Sciancalepore M, Strippoli GF. Trial quality in nephrology: how are we measuring up? *Am J Kidney Dis* 2011; **58**: 335–37.
- 116 Beck LH Jr, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 2009; **361**: 11–21.
- 117 Hoxha E, Kneifler U, Stege G, et al. Enhanced expression of the M-type phospholipase A2 receptor in glomeruli correlates with serum receptor antibodies in primary membranous nephropathy. *Kidney Int* 2012; **82**: 797–804.
- 118 Glassock RJ. The pathogenesis of membranous nephropathy: evolution and revolution. *Curr Opin Nephrol Hypertens* 2012; **21**: 235–42.
- 119 Lash JP, Go AS, Appel LJ, et al, and the Chronic Renal Insufficiency Cohort (CRIC) Study Group. Chronic Renal Insufficiency Cohort (CRIC) Study: baseline characteristics and associations with kidney function. *Clin J Am Soc Nephrol* 2009; **4**: 1302–11.
- 120 Eckardt KU, Bärthlein B, Baid-Agrawal S, et al. The German Chronic Kidney Disease (GCKD) study: design and methods. *Nephrol Dial Transplant* 2012; **27**: 1454–60.
- 121 Benigni A, Morigi M, Remuzzi G. Kidney regeneration. *Lancet* 2010; **375**: 1310–17.