Acute Kidney Injury: Epidemiology and Assessment

5

Rachel M. Hilton

Acute renal failure, now called acute kidney injury (AKI), is common and costly and carries a very high morbidity and mortality. As it is often preventable, identification of at-risk patients and institution of appropriate preventive measures are crucial; rapid recognition and treatment may prevent irreversible nephron loss, even death. Most cases of AKI are initially managed by non-specialist clinicians, often comparatively junior ones; therefore, all clinicians need to be au fait with the initial assessment and management of AKI. Nephrologists need to ensure that referring teams are supported in recognising the symptoms and signs of AKI, requesting and interpreting initial investigations, initiating appropriate treatment and knowing when to refer on to the renal team. This chapter covers the common causes of AKI, defines at-risk populations, outlines the clinical diagnostic approach and highlights ways of predicting risk of AKI.

Definitions and Classifications

The clinical syndrome of AKI is characterised by a sudden decline in glomerular filtration rate (GFR) over a period of hours to days and manifest as retention of creatinine, urea and other metabolic waste products. This traditional description lacks precise definition and fails to highlight the importance of early recognition of this life-threatening condition. Consequently, in 2000, a group of experts from critical care and nephrology came together as the Acute Dialysis Quality Initiative (ADQI) to develop a consensus definition whereby AKI is stratified based on the severity and duration of injury into stages of Risk, Injury, Failure, Loss and End-Stage disease (RIFLE) [1]. The Acute Kidney Injury Network (AKIN) comprising the ADQI group and others later modified this definition [2] based on the recognition that even small changes in serum creatinine are associated with increased mortality. At the same time, the term acute kidney injury (AKI) was introduced to encompass the entire spectrum of renal injury from minor changes in kidney function to dialysis dependency. Most recently, the international guideline group Kidney Disease: Improving Global Outcomes (KDIGO) has agreed a definition and staging system that harmonises the previous systems proposed by both ADQI and AKIN [3]. It is anticipated that this definition and staging system will be adopted globally and will validate future comparisons of the incidence, outcomes and efficacy of therapeutic interventions for AKI. Under the KDIGO classification scheme, AKI is defined as an abrupt (within 48 h to one week) rise in serum creatinine or as a sustained (more than 6 h) reduction in urine output and can be further classified into three stages based on the absolute or relative increase in serum creatinine or duration of reduction in urine output (Table 5.1).

These classifications help define the degree of kidney dysfunction at diagnosis, aid tracking of the clinical course, are widely validated and have been shown to predict outcomes in diverse patient populations and in large international databases. Under all classification schemes, loss of kidney function requiring dialysis for more than 3 months constitutes end-stage kidney disease. For audit, education and prevention consider implementing routine, prospective AKI scoring for hospital inpatients.

Epidemiology

The worldwide incidence of AKI is poorly known because of under-reporting, regional disparities and differences in definition and case mix. Most epidemiological studies have focused on hospital or critical care inpatients, and relatively few have addressed the incidence in the general population. In one large population-based study in Scotland [4], the

R.M. Hilton, MA, PhD, FRCP
Department of Nephrology and Transplantation,
Guy's and St Thomas' NHS Foundation Trust,
Great Maze Pond, London SE1 9RT, UK
e-mail: rachel.hilton@gstt.nhs.uk

M. Harber (ed.), *Practical Nephrology*,
DOI 10.1007/978-1-4471-5547-8_5, © Springer-Verlag London 2014

Table 5.1 KDIGO classification of acute kidney injury [3]

AKI stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of ≥26 μmol/L (0.3 mg/dL) within 48 h or increase to ≥1.5–1.9 × baseline serum creatinine within 1 week	<0.5 mL/kg/h for >6 consecutive hours
2	Increase in serum creatinine to >2.0–2.9 × baseline serum creatinine	<0.5 mL/kg/h for >12 consecutive hours
3	Increase in serum creatinine to >3-fold from baseline or serum creatinine of ≥354 μmol/L [≥4.0 mg/dL] or commenced on renal replacement therapy irrespective of stage	<0.3 mL/kg/h for >24 consecutive hours OR anuria for 12 h

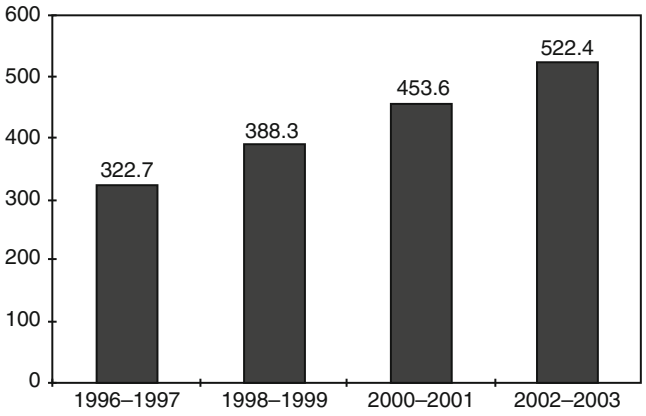

Fig. 5.1 Community-based incidence rates (per 100,000 person-years) of non-dialysis-requiring ARF by calendar year (Reproduced with permission from Hsu et al. [5])

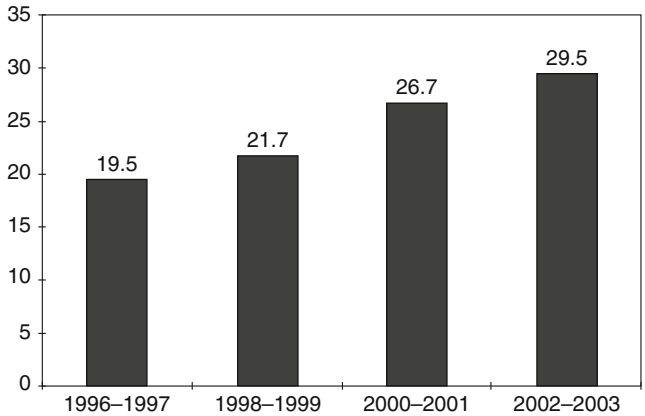

Fig. 5.2 Community-based incidence rates (per 100,000 person-years) of dialysis-requiring ARF by calendar year (Reproduced with permission from Hsu et al. [5])

annual incidence of AKI according to RIFLE criteria was 2,147 per million population, with sepsis as the leading cause. The community-based incidence of AKI is increasing over time. In a different study in Northern California, among members of one of the largest integrated healthcare systems in the USA and using different diagnostic criteria, the annual incidence of AKI was 4,085 per million population [5], more commonly occurring in men and among the elderly (Figs. 5.1 and 5.2).

AKI is an increasingly common cause of acute hospitalisation [6], particularly when superimposed on chronic kidney disease (CKD) (Fig. 5.3). Retrospective studies suggest that the incidence of hospital-acquired AKI varies between 3.2 % if defined by AKIN criteria [7] and 18 % if defined by RIFLE criteria [8] and can be as high as 60 % in patients with severe sepsis [9]. A number of large prospective and retrospective studies have been undertaken which analyse the incidence of AKI in critical care units in various centres. In a large study of more than 120,000 patients admitted to intensive care units across Australia [10], AKI according to RIFLE criteria occurred in 36 % of patients and was associated with a threefold increase in hospital mortality. An even larger study reported on more than 300,000 patients admitted to intensive care in the USA and found the overall AKI incidence using AKIN criteria to be 22 %, mostly AKI stage 1 [11].

Whereas in developed countries AKI occurs predominantly in urban intensive care units in older patients in association with multi-organ failure and sepsis, in rural regions of the developing world, AKI more commonly develops in response to infection (e.g. gastroenteritis or severe infection such as malaria or leptospirosis), obstetric complications or toxins, such as snake bite, and in younger otherwise healthy individuals [12].

For both the community and hospital setting, there are several features that predict a significantly increased risk of AKI (Table 5.2). Given the substantial increased mortality associated with AKI, it is clearly important to have systems in place to identify who is at risk. The awareness, for example, among general medical and surgical teams that an elderly patient with cardiac impairment on an angiotensin-converting enzyme inhibitor (ACEI) undergoing surgery is at significant risk of AKI, is an important first step in prevention of this serious complication.

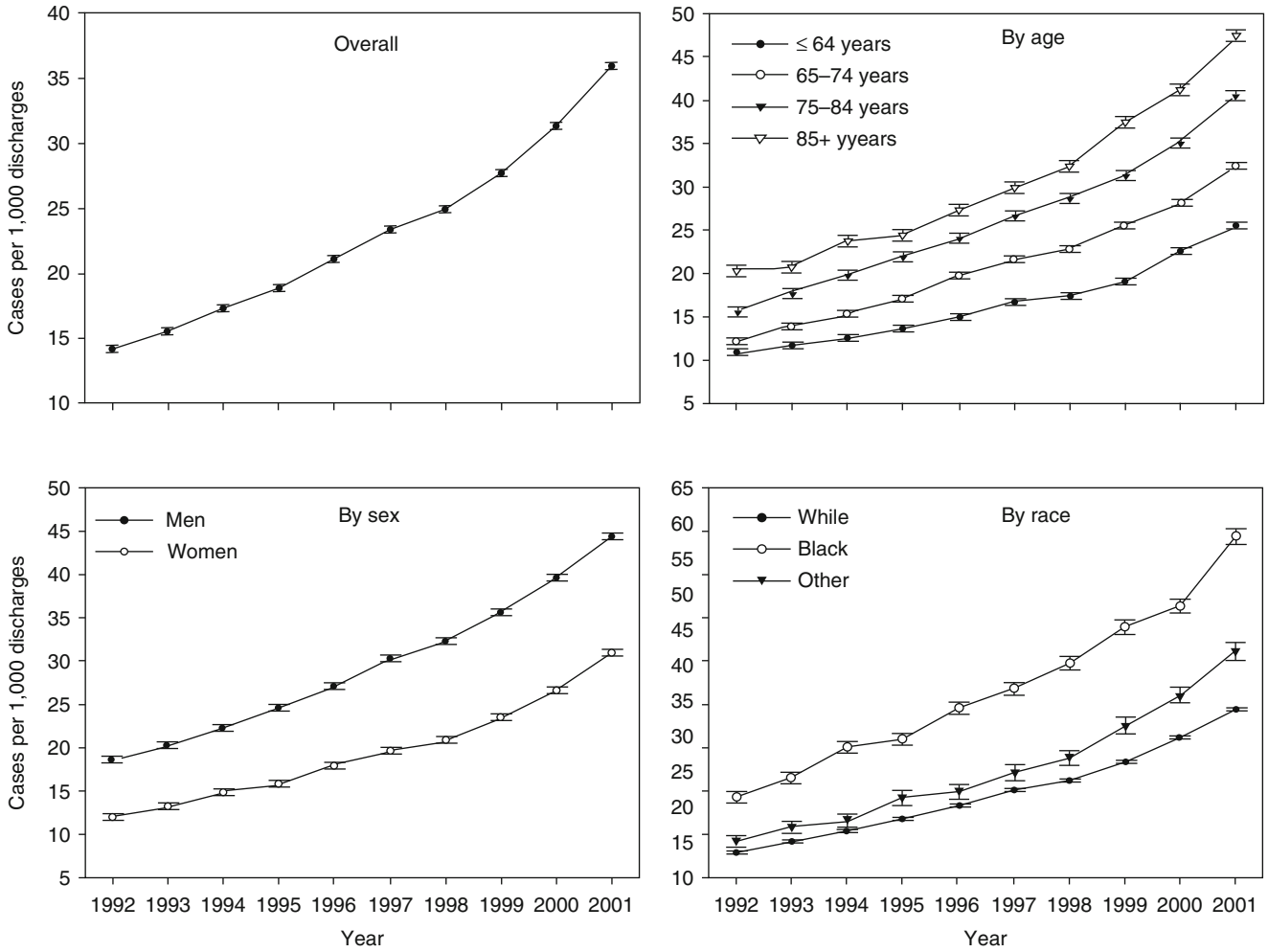

Fig. 5.3 Number of cases of AKI per 1,000 hospital discharges of US Medicare beneficiaries, 1992–2001. I-bars represent Standard Error (Reproduced with permission from Xue et al. [6])

Table 5.2 Risk factors for AKI

1. Pre-existing CKD (especially diabetes, myeloma)
2. Reduced intravascular volume (reduced renal perfusion):
(a) Hypovolaemia (impaired oral intake, haemorrhage, GI losses, renal losses, skin losses)
(b) Reduced effective arterial blood volume (cirrhosis, nephrotic syndrome, third-spacing, e.g. pancreatitis, complex fractures, acute lung injury, peritonitis)
3. Impaired cardiac output (reduced renal perfusion)
4. Old age (reduced GFR, reduced renal reserve, co-morbidity)
5. Sepsis (reduced renal perfusion)
6. Prolonged surgery (any, but especially if involving cross-clamping of the aorta or renal arteries)
7. Jaundice
8. Exposure to toxins:
(a) Endogenous (sepsis), rhabdomyolysis (myoglobin), tumour lysis syndrome (urate), intravascular haemolysis (free haemoglobin), multiple myeloma (light chains)
(b) Exogenous (intravenous contrast and other nephrotoxic agents/drugs; drugs preventing normal renal autoregulation, e.g. ACEI, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory drugs)

Pathophysiology

The susceptibility of the kidney to injury from ischaemia and toxins derives partly from the vulnerability of tubular cells in the outer medulla to ischaemia and hypoxia and partly from the role of the nephron in filtering, concentrating and potentially reabsorbing substances from the tubular lumen that may cause local epithelial cell injury, typically drugs and contrast media.

There are two components that contribute to the acute decrease in GFR in AKI: a "vascular" component and a "tubular" component. Ischaemic injury to the kidney is the most common cause of AKI, but it must be remembered that contributory factors include not only diminished renal blood flow and oxygen and substrate delivery but also a relative increase in oxygen demand by the tubular cells. Acute ischaemia has been shown experimentally to be associated with a loss of renal autoregulation, and in addition, rather than the usual autoregulatory renal vasodilatation that occurs in response to decreased renal perfusion, there is evidence for renal vasoconstriction. Outer medullary congestion is another prominent feature that may worsen the relative hypoxia in the outer medulla and thus potentiate hypoxic injury. As well as intrarenal vasoconstriction, vascular congestion in the outer medulla and activation of tubuloglomerular feedback (the "vascular" component), there is also tubular obstruction, transtubular backleak of filtrate and interstitial inflammation (the "tubular" component). Injured epithelial cells generate and recruit inflammatory and vasoactive mediators that can further compound renal vasoconstriction and inflammation. So tubular injury may be a direct consequence of metabolic pathways activated by ischaemia but is potentiated by inflammation [13].

Key Causes

The causes of AKI can be grouped into those that lead to decreased renal blood flow (prerenal acute kidney injury, 40–70 % of patients), those that lead to direct renal parenchymal damage (intrinsic acute kidney injury, 10–50 % of patients) and those that lead to obstructed flow of urine (postrenal acute kidney injury, 10 % of patients).

Prerenal Acute Kidney Injury

Prerenal causes are the most common and include any condition that leads to under-perfusion of the kidney (Table 5.3). Renal blood flow and GFR remain roughly constant across a wide range of mean arterial pressures due to changes in pre- and post-glomerular arteriolar resistance. This renal autoregulation mainly depends on a combination of pre-glomerular arteriolar vasodilatation, mediated by prostaglandins and nitric oxide, and post-glomerular arteriolar vasoconstriction, mediated by angiotensin II. Drugs that interfere with these mediators may provoke prerenal acute kidney injury in particular clinical settings. The at-risk population includes older people with atherosclerotic cardiovascular disease, those with pre-existing CKD and those with chronic renal hypoperfusion (e.g. cardiac failure, hepatorenal syndrome). In critical care units, the most common cause of AKI is sepsis. In tropical and developing countries, prerenal AKI commonly occurs secondary to dehydration due to diarrhoeal diseases or shock secondary to trauma, affecting a relatively younger population, often children.

Table 5.3 Main causes of prerenal AKI

Causes	Examples
Hypovolaemia	Severe bleeding
	Volume depletion, for example, gastrointestinal fluid losses, burns, polyuria (post-obstructive, over-diuresis, salt-wasting nephropathy, hyperglycaemia, diabetes insipidus)
Hypotension (NB: this may be relative in previously hypertensive patient)	Cardiogenic shock
	Distributive shock ("3rd spacing"), for example, sepsis, anaphylaxis, severe pancreatitis
Reduced renal blood flow	Drugs:
	Nonsteroidal anti-inflammatory drugs (NSAIDs)
	Selective cyclo-oxygenase 2 inhibitors
	Angiotensin-converting enzyme (ACE) inhibitors
	Angiotensin II receptor antagonists
	Renal artery stenosis, occlusion or embolisation
	Hepatorenal syndrome
Decreased effective arterial blood volume	Heart failure
	Liver cirrhosis
	Nephrotic syndrome

Table 5.4 Main causes of intrinsic AKI

Causes	Examples
Glomerular disease	
(a) Inflammatory	Postinfectious glomerulonephritis
	Henoch-Schönlein purpura
	Systemic lupus erythematosus
	Anti-neutrophil cytoplasmic antibody glomerulonephritis
	Anti-glomerular basement membrane disease
	Cryoglobulinaemia
(b) Thrombotic	Disseminated intravascular coagulopathy
	Thrombotic microangiopathy, for example, haemolytic uraemic syndrome
Tubular injury	Ischaemia secondary to prolonged renal hypoperfusion
	Toxins:
	Drugs, for example, aminoglycosides
	Radio contrast
	Snake bite
	Pigments, myoglobin and haemoglobin
	Heavy metals, for example, cisplatinum
	Metabolic, for example, hypercalcaemia and immunoglobulin light chains
	Crystals, for example, urate, oxalate and some medications
Interstitial injury	Drug induced, for example, NSAIDs and antibiotics
	Infiltrative, for example, lymphoma
	Granulomatous, for example, sarcoidosis and tuberculosis
	Infection related, for example, postinfective and pyelonephritis
Vascular injury	Vasculitis, usually ANCA associated
	Cryoglobulinaemia
	Polyarteritis nodosa
	Thrombotic microangiopathy
	Cholesterol emboli
	Renal artery or renal vein thrombosis

Intrinsic Acute Kidney Injury

Intrinsic acute kidney injury may be caused by conditions affecting the glomeruli, renal tubules, interstitium or vasculature (Table 5.4). The most important causes are listed here.

Postrenal Acute Kidney Injury

It is important to recognise obstructive nephropathy because rapid diagnosis and prompt intervention can result in improvement or even complete recovery of kidney function (Table 5.5).

Table 5.5 Main causes of postrenal AKI (see Chap. 37)

Causes	Examples
Intrinsic	Intraluminal, for example, stone, blood clot and papillary necrosis
	Intramural, for example, urethral stricture and bladder tumour
Extrinsic	Prostatic hypertrophy or malignancy
	Autonomic bladder
	Anticholinergics
	Constipation, immobility, pain
	Pelvic malignancy
	Retroperitoneal fibrosis
	Radiation fibrosis
	Abdominal compartment syndrome[a]

[a]Abdominal compartment syndrome is an under-recognised contributor to AKI when the peritoneal cavity pressure is high. The mechanism for causing a fall in GFR is not known but is likely to be due to a combination of renal hypoperfusion and renal vein congestion [14]

Clinical Approach to Diagnosis

The diagnostic approach to a patient with AKI requires a careful history, scrutiny of the medical notes, drug charts, observations charts and anaesthetic records, thorough physical examination and interpretation of appropriate investigations including laboratory tests and imaging. It is vital to obtain historical blood tests, urine analysis and recent drug history where possible.

For each patient with apparent AKI, the following questions need to be considered:

1. Is this acute kidney injury or chronic kidney disease?
2. What is the intravascular volume status of the patient?
3. Has obstruction been excluded?
4. Is there evidence of intrinsic AKI other than acute tubular injury?

History and Examination

Although there may be nonspecific symptoms, renal impairment is often asymptomatic and may only be diagnosed by laboratory tests. However, patients with chronic kidney disease may have a long history of symptoms such as fatigue, nausea, nocturia or itch (Table 5.6). A history of underlying chronic disease such as diabetes, hypertension or peripheral vascular disease may be present, whereas patients with AKI

Table 5.6 Some specific conditions associated with AKI

Diabetes	Hypovolaemia, renal losses HONK and DKA; urosepsis, acute sepsis and pyelonephritis; obstruction, secondary to sloughed papilla (papillary necrosis), and secondary to autonomic bladder Underlying (often subclinical) diabetic nephropathy is a significant contributing risk factor for AKI. NB: pyelonephritis may be subacute and asymptomatic
Gastrointestinal	Acute diarrhoeal illnesses (hypovolaemia +/− sepsis), diarrhoea-associated HUS, hypovolaemia secondary to high output ileostomy, obstruction secondary to stones in short bowel Acute oxalate nephropathy (pancreatic insufficiency or short bowel), interstitial nephritis secondary to sulphasalazines in inflammatory bowel disease (IBD) Chronic diarrhoea often associated with malnutrition and a low creatinine belies a poor GFR secondary to multiple AKI events IBD may have underlying amyloid (proteinuria); acute oxalate nephropathy can cause rapid AKI and is important to diagnose (check plasma oxalate levels or oxalate on phase contrast microscopy of biopsy)
Liver disease	Reduced effective arterial blood volume: 1. Hepatorenal syndrome 2. Variceal haemorrhage 3. Hypovolaemia post-paracentesis 4. Over-diuresis 5. Hypoalbuminaemia 6. Fulminant hepatitic failure any cause Abdominal compartment syndrome Infections: Sepsis, e.g. spontaneous bacterial peritonitis Leptospirosis, Legionnaire's disease, Hantavirus, Hepatitis B and C, etc. Drugs Paracetamol, rifampicin, isoniazid, azathioprine, tetracycline, etc. Toxins Amanita phalloides (mushroom poisoning), hydrotetracarbon inhalation, etc. Jaundice and reduced effective arterial blood volume make patients with chronic liver disease exquisitely sensitive to AKI from other insults such as hypovolaemia, sepsis or nephrotoxic drugs. Abdominal compartment syndrome is an under-recognised contribution to AKI and should be suspected in anyone with a tense abdomen
Cardiovascular	Acute coronary syndrome: 1. Myocardial stunning/decreased cardiac output 2. Contrast nephropathy 3. Acute cholesterol emboli syndrome 4. Renal arterial embolism Chronic heart failure: Hypoperfusion due to reduced cardiac output Over-diuresis Atherosclerotic renal artery stenosis Takayasu's aortitis and middle aorta syndrome Surgery involving cross-clamping suprarenal aorta or renal arteries Infective endocarditis IVC thrombosis extending to renal vein Renal vein thrombosis and pulmonary emboli AKI common in the setting of large myocardial infarction, chronic heart failure is often associated with underlying CKD, and these patients are very sensitive to hypovolaemia particularly in the context of renin:angiotensin blockade. An abrupt deterioration in renal function may be due to renal artery or vein thrombosis, often silent and only detectable by MAG-3 scan

Table 5.6 (continued)

Cancer	Endogenous toxins: 1. Hypercalcaemia 2. Tumour lysis syndrome (hyeruricaemia) 3. Light-chain nephropathy (myeloma) Exogenous toxins: Cisplatin, methotrexate, ifosfamide, etc. Radiation (fibrosis and TMA) Reduced renal perfusion, e.g. hypovolaemia nausea/vomiting/anorexia Drug-induced cardiomyopathy Direct infiltration: Lymphoma (and PTLD), chronic lymphocytic leukaemia, acute lymphoblastic leukaemia Obstruction Glomerular lesions Rapid progressive glomerulonephritis Minimal change GN (lymphoma) Membranous GN (solid organ malignancy) TMA
Pulmonary-renal syndrome (AKI and acute pulmonary impairment)	1. Heart failure or fluid overload (AKI and pulmonary oedema) 2. Infective endocarditis 3. Pulmonary emboli secondary to renal vein thrombosis 4. Vasculitis: Goodpasture's syndrome GCA Microscopic polyangiitis Churg-Strauss syndrome Crescentic IgA and Henoch-Schönlein purpura Cryoglobulinaemia Systemic lupus erythematosus 5. Infections: Bacterial: Legionnaire's disease, pneumococcal pneumonia, hantavirus, HIV, tuberculosis 6. Sarcoidosis 7. Any cause multi-organ failure (ARDS) The commonest presentation of pulmonary and renal failure is pulmonary oedema in the context of CKD or ESRF, and this can mimic many lung pathologies Diagnosing the much rarer vasculitic pulmonary-renal syndrome requires a high index of suspicion especially if active urine deposit. Urine microscopy and *urgent* immunology are critical
Blood-borne viruses	Hepatitis C: Cryoglobulinaemia (+/– MCGN), interstitial nephritis Hepatitis B: Cryoglobulinaemia (+/– MCGN), membranous nephropathy, interstitial nephritis, polyarteritis nodosa HIV Thrombotic microangiopathy, HIVAN, immune complex GN, vasculitis, MCGN, membranous GN Tubular toxicity: foscarnet, tenofovir, iv pentamidine, cidofovir, amphotericin, aminoglycosides. Crystal nephropathy : acyclovir, indinavir, sulphadiazine
Pregnancy	TMA: (a) eclampsia, (b) HUS, (c) HELLP, (d) acute fatty liver of pregnancy Septic shock (following septic abortion) Hypovolaemia (hyperemesis gravidarum) Obstruction Pyelonephritis Exacerbation of autoimmune disease

(continued)

Table 5.6 (continued)

Tropical AKI	Diarrhoeal diseases
	Haemolytic uraemic syndrome (has replaced diarrhoeal diseases as the commonest cause of AKI in children in several tropical countries)
	Intravascular haemolysis and G6PD deficiency (acute haemolysis in individuals deficient in G-6-PD is a frequent cause of AKI in some ethnic populations in tropical countries and is the usual cause of AKI in typhoid as ciprofloxacin is widely used for this condition)
	Infection, e.g. malaria, leptospirosis, typhoid
	Plant, animal and chemical toxins:
	Snake bite (common cause of AKI, e.g. in Southern India)
	Bee, wasp and hornet stings and spider bites
	Mushroom poisoning
	Heat stroke
	Obstetric AKI (remains a major preventable cause of AKI)
Haematological disease	AL amyloidosis
	Myeloma:
	1. Dehydration
	2. Hypercalcaemia
	3. Infection
	4. NSAIDs
	5. Myeloma cast nephropathy
	Sickle-cell disease (AKI can occur in conjunction with any other complication in sickle-cell disease, most notably sepsis):
	1. Prolonged painful crises
	2. Acute chest syndrome
	3. NSAIDs
	4. Rhabdomyolysis
	5. Papillary cell necrosis
	Paroxysmal nocturnal haemoglobinuria
	Acute and chronic leukaemias
	Tumour lysis syndrome
	Bone marrow transplantation (AKI is one of the most frequent complications of bone marrow transplantation, usually occurring within the first month):
	1. Sepsis
	2. Hypovolaemia
	3. Nephrotoxic drugs
	4. Obstructive uropathy (tumour, calculi)
	5. Tumour lysis syndrome
	6. Haemolytic uraemic syndrome

are more likely to have an acute illness. The most useful and important clue comes from previous creatinine measurements. It is therefore critical to retrieve historical results and imaging from other sources if possible, as this indicates whether the kidney impairment is new or pre-existing and gives an idea of the rate of decline in kidney function. There may be a history of excessive fluid loss from haemorrhage, diarrhoea, vomiting or sweating, coupled with insufficient fluid replacement, especially in patients who are unable to take oral fluids. On direct questioning, there may be constitutional symptoms indicative of a systemic autoimmune disease, infection or malignancy. Current and new medication use maybe relevant, particularly antibiotics, nonsteroidal anti-inflammatory drugs and proton pump inhibitors, because these can cause acute interstitial nephritis. Almost any drug may cause an idiosyncratic reaction, sometimes many months after initiation. A history of illicit drug use and herbal remedies may also be pertinent. It is important to enquire about previous kidney stones or symptoms of bladder outflow obstruction such as hesitancy, frequency and nocturia as well as abnormalities in the urine such as haematuria, dark or offensive urine. Complete anuria is unusual in early AKI and suggests (1) urinary tract obstruction, (2) renal infarction/profound shock, (3) urinary leak or (4) Goodpasture's syndrome.

The focus of clinical examination should be to:

(a) Assess the effective arterial blood volume
(b) Identify any systemic disease
(c) Exclude lower urinary tract obstruction (i.e. palpable bladder or ballotable kidney)
(d) Identify any intrinsic renal disease (i.e. urine dipstick)

A careful assessment of the patient's fluid status, in particular intravascular volume, is essential. Pulse rate and volume, *relative* blood pressure, postural blood pressure, JVP and peripheral perfusion are important and useful clinical signs (reduced skin turgor and dry mucous membranes may be unhelpful signs in older people). Response to fluid challenges, i.e. sustained or transient rise in blood pressure or central venous pressure following a bolus of fluid, is very helpful in determining whether a patient is intravascularly replete. Examination may reveal features of underlying systemic disease, such as skin rashes, scleritis, episcleritis, nasal bridge collapse, alopecia, mouth ulcers, arthritis or stigmata of endocarditis. You should consider cholesterol embolism in the differential diagnosis of AKI in older patients following interventions such as angiography, vascular surgery, thrombolysis or anticoagulation. This is characterised by the triad of livedo reticularis, AKI and eosinophilia, frequently accompanied by signs of peripheral ischaemia in a patient with signs of macrovascular disease such as vascular bruits [15]. The onset is typically 1–4 weeks after the procedure, and patients may have forgotten about the procedure by the time they present.

Investigation

Tailor investigations to individual circumstances. It is not necessary to request a full battery of immunological tests in a patient with postoperative acute tubular injury or urinary tract obstruction, but this would be appropriate if uncertain about the diagnosis or if there was suspicion of an inflammatory condition. However, it is critical to ensure that a urine dipstick test and microscopy is done on all patients with AKI to avoid missing an inflammatory process (see Chap. 2 Henderson/Harber) (Table 5.7). Blood or protein on dipstick or dysmorphic red cells or red cell casts strongly suggests glomerulonephritis. Eosinophils on microscopy suggest acute interstitial nephritis; both situations require prompt

Table 5.7 Key investigations in acute kidney injury (italic for essential initial tests in patient with unexplained AKI)

	Test	Comment
Urinalysis	*Dipstick for blood and/or protein*	Suggestive of a renal inflammatory process
	Microscopy for cells, casts, crystals	Red cell casts diagnostic in glomerulonephritis
Biochemistry	*Serial urea, creatinine, sodium, potassium, calcium, phosphate, urate, serum bicarbonate*	Important metabolic consequences of acute renal failure include hyperkalaemia, metabolic acidosis, hypocalcaemia, hyperphosphataemia
	(If sick) blood gas analysis and lactate	Markedly elevated creatine kinase and myoglobinuria suggestive of rhabdomyolysis
	Creatine kinase, myoglobinuria	Non-specific marker of infection or inflammation
	C-reactive protein	Immune paresis, monoclonal band on serum protein electrophoresis and Bence Jones proteinuria suggestive of myeloma
	Serum immunoglobulins, serum protein electrophoresis, Bence Jones proteinuria	
Haematology	*Full blood count, blood film*	Eosinophilia may be present in acute interstitial nephritis, cholesterol embolisation or vasculitis
	Coagulation studies	Thrombocytopenia and red cell fragments suggestive of thrombotic microangiopathy
		Disseminated intravascular coagulation associated with sepsis
Immunology (if haematuria/proteinuria)	Antinuclear antibody (ANA)	ANA positive in systemic lupus erythematosus (SLE) and other autoimmune disorders; anti-double-stranded DNA antibodies more specific for SLE
	Anti-double-stranded DNA antibodies	Associated with systemic vasculitis
	Anti-neutrophil cytoplasmic antibody (ANCA)	c-ANCA and anti-PR3 antibodies associated with GPA granulomatosis; p-ANCA and anti-MPO antibodies present in microscopic polyangiitis
	Antiproteinase 3 (PR3) antibodies	Low in SLE, acute postinfectious glomerulonephritis, cryoglobulinaemia
	Antimyeloperoxidase (MPO) antibodies	Present in Goodpasture's disease
	Complement levels	Elevated following streptococcal infection
	Anti-glomerular basement membrane antibodies	
	Antistreptolysin O and anti-DNAse B titres	
Virology	*Hepatitis B and C*; *HIV*	Important implications for infection control within the dialysis area
Radiology	*Renal ultrasound*	Renal size, symmetry, evidence of obstruction
	Chest X-ray	May reveal pulmonary oedema or cardiomegaly
Histopathology	Renal biopsy	May be performed if clinical and laboratory assessment suggests systemic disease or if the diagnosis is unclear

specialist referral. Positive haematuria on dipstick in the absence of RBC on microscopy strongly suggests a pigment nephropathy, i.e. either rhabdomyolysis or significant intravascular haemolysis.

Renal ultrasound is non-invasive, cheap and absolutely critical for (1) excluding obstruction (upper or lower urinary tract), (2) differentiating between acute (normal size) and chronic kidney disease (small) (with the caveat that CKD secondary to diabetes or amyloid may be associated with normal or large kidneys), (3) cortico-medullary differentiation (CMD) (bright kidneys with loss of CMD and thinning of cortex imply CKD and (4) Doppler confirmation of arterial and venous flow. Ultrasound may also identify other causes: multiple cysts of APKD, heterogeneity consistent with pyelonephritis, and scarring or very bright kidneys in acute crystal nephropathy. It is recommended [16] that all cases of apparent AKI should have a renal ultrasound within 24 h, and this should be within 12 h in the setting of urosepsis.

Special Areas

Children

In developing countries, AKI is a disease of the young and children, in whom volume-responsive "prerenal" mechanisms are common [17] and AKI-related mortality is very high despite commonly being due to reversible conditions such as post-streptococcal glomerulonephritis, malaria and diarrhoeal illnesses [18]. In developed countries, AKI is approximately 20-fold less common in children than in adults. Special considerations in children include a higher likelihood of acute obstructive uropathy due to congenital malformations such as imperforate prepuce, urethral stricture, prune belly syndrome, and posterior urethral valves. Other causes of AKI that are relatively more common in children include microangiopathies due to underlying damage to kidney endothelial cells, particularly diarrhoea-associated haemolytic uraemic syndrome (HUS) arising from endothelial damage by bacterial endotoxin such as the toxin expressed by *Escherichia coli* 0157 [19].

Pregnancy (See Chapter on "Pregnancy and Renal Disease")

AKI in pregnancy may be due to any disorder that can cause AKI in the general population, but there are additional complications characteristic of each trimester of pregnancy that can result in AKI. During the first trimester, the most common causes are hypovolaemia due to hyperemesis gravidarum or acute tubular injury following a septic abortion. Later in pregnancy a variety of less common disorders can cause AKI. These include acute pyelonephritis, which occurs in 1–2 % of pregnancies and can be associated with hypovolaemia and septic shock. The gravid uterus may cause ureteric obstruction, particularly if the pregnancy is multiple or if there is polyhydramnios. Endothelial changes in pregnancy may contribute to a number of conditions including a predisposition to thrombotic microangiopathies (TMA) such as haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura [20]. During the third trimester, catastrophic hypotensive events such as placental abruption or severe post-partum haemorrhage may result in acute cortical necrosis from severe ischaemic injury, and globally, this remains an important cause of AKI. Acute fatty liver of pregnancy is an extremely rare variant of pre-eclampsia and may be associated with AKI or multi-organ failure. In developing countries, AKI remains a common and potentially preventable cause of maternal mortality, which varies between 6 and 30 % in reported series [21].

The Elderly

The incidence of AKI is highest in elderly patients [5], who make up an ever-growing proportion of the general population. Pre-existing CKD is a powerful risk factor although few studies have focused on this area [22]. In older people, the commonly used signs to gauge volume depletion can be misleading. Severely ill patients may have gross oedema while at the same time being intravascularly depleted. Reduced skin turgor and a dry mouth are increasingly common in older people and cannot be relied upon to indicate dehydration. More useful signs include postural hypotension and a low jugular venous pressure. The limitations of serum creatinine to estimate GFR are much more pronounced in the elderly, including its dependence on muscle mass and the presence of multiple drug use and co-morbidities [23]. Older age is also associated with a greater risk of non-recovery of renal function back to baseline, which, given the increasing incidence of AKI, raises significant public health concerns about the absolute number of elderly people developing incident CKD.

Rhabdomyolysis

Rhabdomyolysis was first described in the victims of crush injury during the 1940–1941 World War II bombing raids in London, and its complications remain significant problems for those injured in disasters such as earthquakes and bombings. Rhabdomyolysis is characterised by the leakage of

muscle-cell contents, including electrolytes, myoglobin, creatine kinase and other proteins, into the circulation. High circulating plasma myoglobin levels (lasting for only 1–6 h) can cause acute tubular injury and AKI. The cause of rhabdomyolysis is often self-apparent (Table 5.8), but if not it may occasionally be due to an inherited muscle enzyme deficit [24]. AKI complicates up to 50 % of cases of severe rhabdomyolysis and substantially worsens the prognosis [25]. Rhabdomyolysis is a relatively common cause of AKI, accounting for 8–15 % of cases in the USA [26]. The classic presentation is with myalgia, limb weakness, pigmenturia due to myoglobinuria (very transient) with positive dipstick for blood but without haematuria on microscopy and a markedly raised CK (in tens of thousands, starting 2–12 h post insult and peaking between 1 and 3 days). Serum potassium is usually raised (in the presence of renal impairment often dangerously so), phosphate levels are disproportionately high for the degree of renal impairment and calcium levels are low (in part due to sequestration by damaged muscle). Occasionally, patients will present with AKI several days after the event with an unremarkable CK level: (1) subsequent hypercalcaemia (2) calcification in the affected muscles on X-ray or (3) a bone scan showing uptake in the muscles may make the diagnosis (Fig. 5.4).

Table 5.8 Causes of rhabdomyolysis

Direct injury or hypoxia	Direct trauma, crush injury, burns, frost-bite, electrocution Ischaemia secondary to immobility-falls, coma (medical or drug induced), prolonged surgery Ischaemia secondary to acute vascular insufficiency or compartment syndrome	
Excessive muscle activity	Grand mal fit, status epilepticus, acute psychosis, prolonged myoclonus, dystonia, status asthmaticus Excessive exercise e.g. marathon running, military training of new recruits	NB clinically relevant rhabdomyolysis secondary to excessive exercise *usually* only occurs in the presence of dehydration (or heat stroke) unless underlying medical predisposition or drug exposure
Muscle enzyme defects	Deficiency of glycol(geno)lytic enzymes 1. Myophosphorylase deficiency (McArdle's) 2. Phosphorylase kinase deficiency 3. Phosphorylase mutase deficiency 4. Lactate dehydrogenase deficiency Abnormal lipid 1. Carnitine palmitoyltransferase deficiency 2. Carnitine deficiency Miscellaneous 1. Neuroleptic malignant syndrome 2. Malignant hyperthermia 3. Myoadenylate deamine deficiency 4. Idiopathic rhabdomyolysis syndrome	Rare causes, usually presenting before the age of 20. Look out for history of 1. Exercise intolerance 2. Cramps 3. Intermittent dark urine 4. Family history (most autosomal recessive) 5. More than one episode of rhabdomyolysis with minor exercise or no obvious precipitant If suspicious refer for muscle biopsy Hyperthermia or hypothermia
Metabolic	1. Hypokalaemia 2. Hypophosphataemia 3. Hyponatraemia 4. Hypothyroidism 5. Diabetic ketoacidosis 6. Hyperosmolar non-ketotic diabetic coma	Hypokalaemia, hypophosphataemia and hyponatraemia important predisposing risk factors
Infectious	1. Viral (Influenza, adenovirus, echovirus, HIV, EBV, Coxsackie, enterovirus) 2. Bacterial (staphylococcus aureus, streptococcus pneumoniae, salmonella) all can cause direct bacterial myositis (thyphoid, shigella, *E. coli*, leptospirosis, legionella, chlostridium perfinges)	

(continued)

Table 5.8 (continued)

Drugs	1. Statins and fibrates 2. Chronic and acute alcohol abuse 3. Cocaine 4. Heroin 5. Amphetamines 6. Theophylline 7. Antibiotics 8. Barbiturates 9. Abrupt withdrawal of L-dopa in Parkinson's syndrome	Risk of lipid lowering myositis increased with dual fibrate/statin therapy, dose, concomitant renal or liver disease, hypothyroidism Also inhibitors of cytochrome p450 macrolide antibiotics, warfarin, cyclosporine, azoles, digoxin (Fluvastatin, pravastatin and atorvastatin are metabolised independently of cytochrome p450 and therefore lower risk)
Toxins	1. Snake bite 2. Hornet stings 3. Spider bite 4. Scorpion 5. Hemlock 6. Not forgetting quail fed on hemlock or hellebore	Alcohol is a significant risk factor in part because of associated electrolyte abnormalities and risk of hypothermia and crush injury
Autoimmune myositis	1. Polymyositis 2. Dermatomyositis	Check autoimmune screen including Anti-JO-1

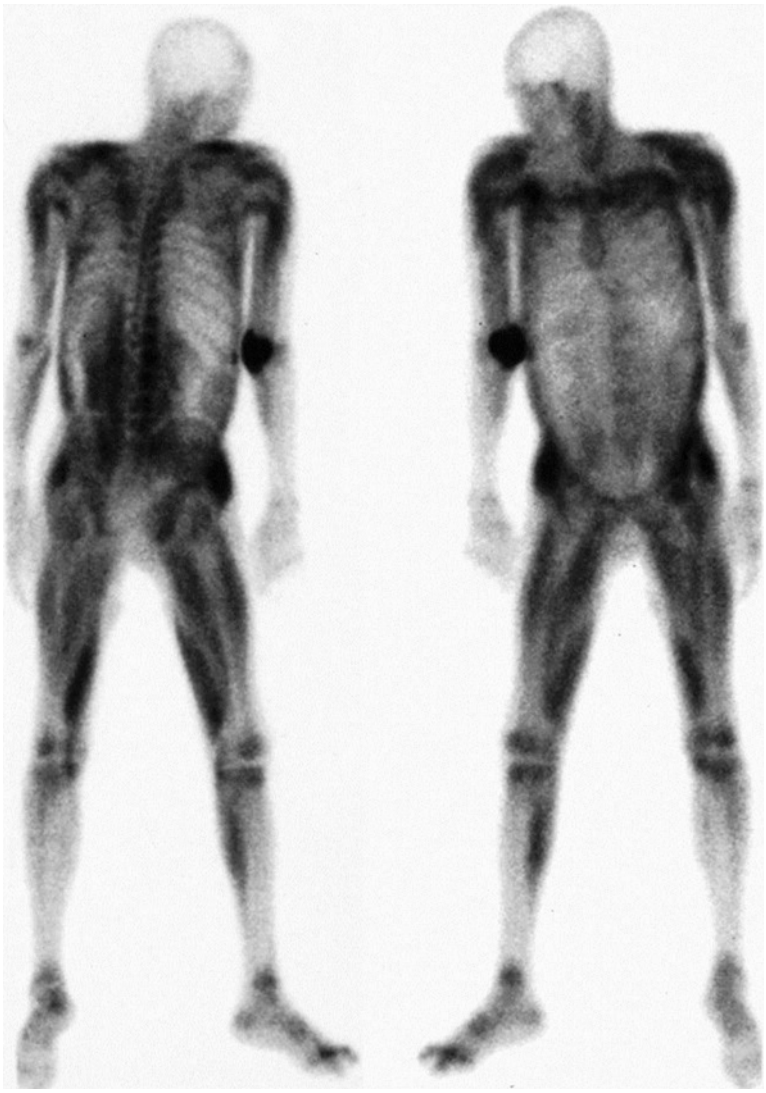

Fig. 5.4 Rhabdomyolysis visualised with a Tc99-labelled diphosphonate bone scan. Posterior (*left*) and anterior (*right*) views (Reproduced with permission from Walsh and Fan [27])

Contrast Nephropathy

Contrast-induced AKI is an important complication in the use of iodinated contrast media and is the third commonest cause of hospital-acquired AKI [28]. Patients at particular risk include those with (1) pre-existing renal impairment, (2) diabetes mellitus, (3) volume depletion, (4) haemodynamic instability, (5) those receiving other nephrotoxic medications or (6) multiple doses of contrast and (7) large volumes of contrast (8) use of hyperosmolar contrast. These risk factors have an additive effect [29]. In high-risk patients, alternative imaging should be considered where possible, but otherwise, the patient should be pre-hydrated, and the lowest volume necessary of nonionic iso-osmolar contrast medium should be used.

Nephrotoxic Drugs

Administration of nephrotoxic drugs has been implicated as a causative factor in up to 25 % of all cases of severe AKI in critically ill patients [30]. There are many drugs with nephrotoxic potential (see Chap. 55), and it is very important to ascertain exactly what drugs, prescribed or illicit, a patient has received and when. Aminoglycoside treatment is relatively commonly associated with nephrotoxicity, occurring in 10–20 % of cases. Aminoglycosides are non-protein bound, primarily cleared by glomerular filtration, then transported into proximal tubular cells where they accumulate and induce cell death. Risk factors for nephrotoxicity include high peak serum levels, cumulative dose and duration and frequency of administration. Proximal tubular cell uptake of aminoglycosides is saturable; therefore, single large doses permit more of the drug to be excreted without undergoing tubular resorption, so reducing cell injury. Numerous meta-analyses have shown similar clinical efficacy with once-daily aminoglycoside dosing, though none has shown a significant reduction in nephrotoxicity [30]. Amphotericin B has for decades been the antifungal drug of choice for critically ill patients because of its low cost and broad spectrum of activity. However, it is highly nephrotoxic with renal dysfunction reported in up to 80 % of patients, the risk relating to cumulative dose [31]. Over the last few years, randomised trials have shown that lipid-based formulations of amphotericin B are significantly less nephrotoxic.

Cancer

AKI is a common complication in patients with cancer. The development of AKI is associated with poor prognosis, although early recognition and treatment are associated with better outcomes [32]. It is difficult to assess the overall prevalence, but studies carried out in specific diseases such as multiple myeloma have shown that 15–30 % of patients have evidence of renal impairment [33]. Important risk factors are dehydration, use of nephrotoxic drugs, pre-existing renal impairment and large tumour burden. Common causes include those resulting from the malignancy itself (e.g. obstruction or infiltration, cast nephropathy in multiple myeloma, paraneoplastic syndromes such as hypercalcaemia), those resulting from treatment (e.g. nephrotoxic drugs, tumour lysis syndrome) and general causes (e.g. volume depletion, sepsis, radiocontrast). Tumour lysis syndrome (TLS) deserves special mention as an oncological emergency most often seen in patients with bulky, rapidly proliferating and treatment-responsive lymphoproliferative malignancies (e.g. acute leukaemias and high-grade non-Hodgkin lymphomas such as Burkitt's lymphoma) after chemotherapy, radiation or corticosteroids. TLS may occur spontaneously in the absence of any treatment but is rare in patients with solid tumours. It is particularly important to identify those at risk, especially so in those with pre-existing renal impairment and monitor their potassium and renal function closely. Risk factors and clinical markers of TLS are shown in Table 5.9 and reviewed in reference [34].

Table 5.9 Risk factors and clinical features of tumour lysis syndrome

Risk Factors for tumour lysis syndrome:
1. High tumour burden (bulky tumour or extensive metastases)
2. High cell lysis potential (rapidly proliferating tumour – LDH is a surrogate marker for this; high cancer-cell sensitivity to therapy; intensity of therapy)
3. Pre-existing patient factors (older age; renal impairment; dehydration; acidic urine; hypotension; nephrotoxic drugs)
4. Inadequate supportive care (inadequate hydration; lack of allopurinol or rasburicase prophylaxis)
Clinical markers of tumour lysis syndrome:
1. Hyperuricaemia (uric acid >0.4 mmol/L)
2. Hyperphosphataemia (serum phosphate >1.5 mmol/L in adults; >2.1 mmol/L in children)
3. Rapid (sometimes life-threatening) rise in potassium (serum potassium >6.0 mmol/L)
4. Hypocalcaemia (corrected calcium <1.75 mmol/L; ionised calcium <0.3 mmol/L)
5. Raised lactate dehydrogenase
6. Acute kidney injury

Outcomes

AKI is a powerful predictor of important clinical outcomes such as hospital mortality, need for renal replacement therapy and prolonged hospital stay in critically ill patients [35]. In uncomplicated AKI, reported mortality rates can be as high as 10 % [36, 37]. In contrast, patients presenting with AKI and multi-organ failure have reported mortality rates of over 50 %. If renal replacement therapy is required, the mortality rate rises further to as high as 80 % [38, 39]. Even

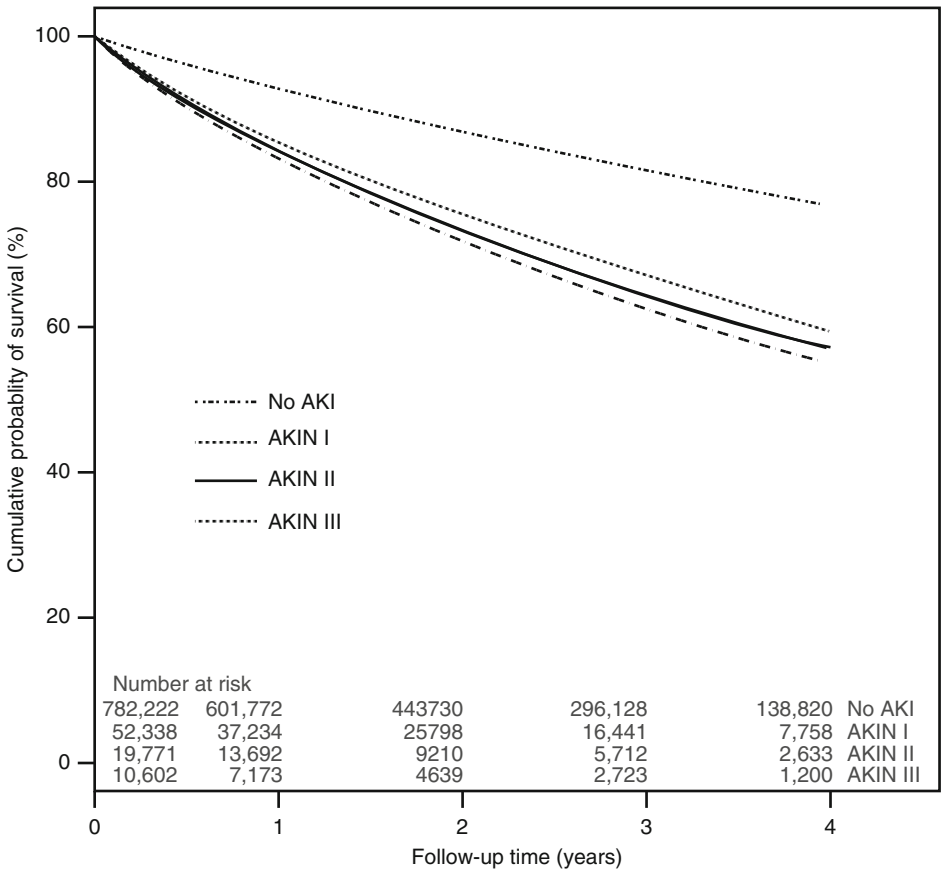

Fig. 5.5 Severity of AKI is associated with increasing risk for death (Reproduced with permission from Lafrance and Miller [40])

milder forms of AKI, not just dialysis-dependent acute renal failure, are associated with excess mortality (Ref. [4] and Fig. 5.5), so recognition and treatment of even very early AKI is likely to improve outcomes. Although long considered a completely reversible syndrome, a wealth of data from experimental and clinical studies indicates that AKI may result in permanent kidney damage (i.e. CKD) (Ref. [41] and Fig. 5.6) and may also result in damage to non-renal organs. A recent meta-analysis identifies AKI as an independent risk factor for CKD, end-stage kidney disease, death and other important non-renal outcomes such as congestive heart failure [42]. There remain considerable challenges in the optimal management of AKI to reduce mortality and improve outcomes, and more research is urgently needed. Tools to predict prognosis in AKI are also much needed, and key advances in this area are likely to come from the rapidly developing field of AKI biomarkers.

Summary

With an ageing population and an increasing prevalence of CKD, heart failure and other morbidities, it seems likely that the incidence of AKI will continue to rise. Although often reversible, AKI has very significant short- and medium-term implications for the individual, and for those where dialysis is not available or tolerated, it may be fatal. Given that many of the multiple risk factors for AKI are predictable, it is beholden on clinicians (and the nephrologists supporting them) to have robust systems in place to prevent, identify early and treat AKI.

Information Resources for Patients

National Kidney and Urologic Diseases Information Clearinghouse (kidney.niddk.nih.gov/index.htm)—US website with information about diseases of the kidneys and urological system for patients, families, healthcare professionals and the general public.

Patient.co.uk (www.patient.co.uk) – an online medical resource supplying evidence based information on a wide range of medical and health topics to patients and health professionals.

Renalinfo (www.renalinfo.com/uk/en/)—Offers help, advice, and support to people being treated for kidney failure.

Royal Infirmary of Edinburgh Renal Unit (http://www.edren.org/pages/edreninfo.php)—Source of information about kidney diseases for patients and non-specialist doctors.

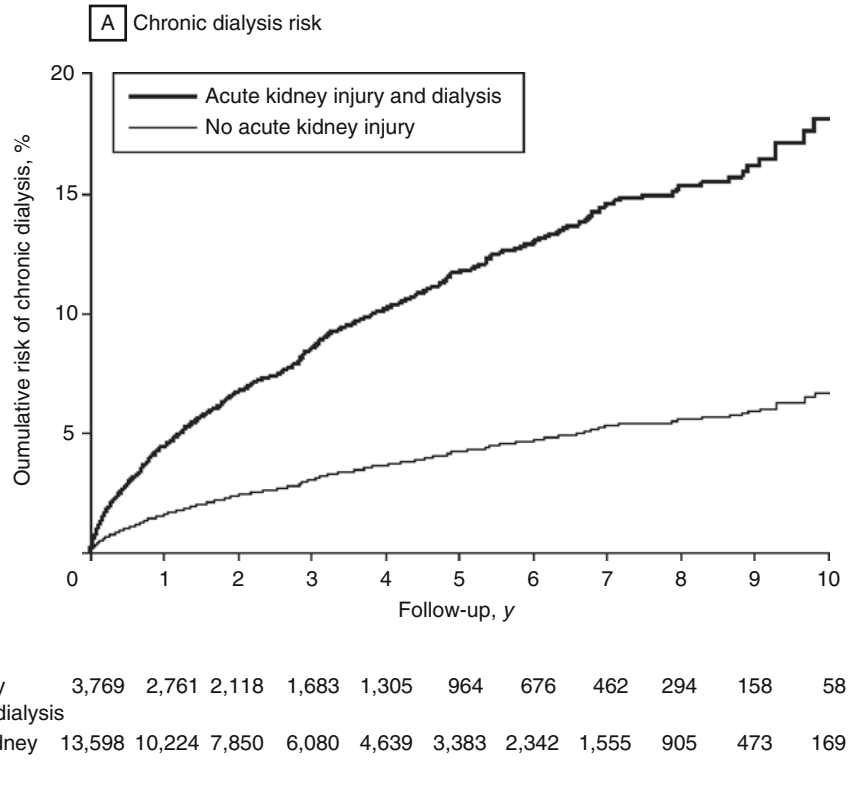

Fig. 5.6 Risk of chronic dialysis in association with acute kidney injury and dialysis during index hospitalisation (Reproduced with permission from Wald et al. [41])

References

1. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, 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(4):R204–12.
2. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
3. Kidney disease: improving global outcomes. Clinical practice guideline on acute kidney injury. 2011. www.kdigo.org.
4. 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;18:1292–8.
5. Hsu CY, McCulloch CE, Fan D, Ordoñez JD, Chertow GM, Go AS. Community-based incidence of acute renal failure. Kidney Int. 2007;72:208–12.
6. 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.
7. Fang Y, Ding X, Zhong Y, et al. Acute kidney injury in a Chinese hospitalized population. Blood Purif. 2010;30:120–6.
8. Uchino S, Bellomo R, Goldsmith D, et al. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med. 2006;34:1913–7.
9. Murugan R, Karajala-Subramanyam V, Lee M, et al. Acute kidney injury in nonsevere pneumonia is associated with an increased immune response and lower survival. Kidney Int. 2010;77:527–35.
10. Bagshaw SM, George C, Bellomo R. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. Nephrol Dial Transplant. 2008;23:1569–74.
11. Thakar CV, Christianson A, Freyberg R, et al. Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. Crit Care Med. 2009;37:2552–8.
12. 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.
13. Schrier RW, Wang W, Poole B, Mitra A. Acute renal failure: definitions, diagnosis, pathogenesis, and therapy. J Clin Invest. 2004; 114(1):5–14.
14. World Society of Abdominal Compartment Syndrome. http://wsacs.org/. Accessed 13 Mar 2012.
15. Dupont PJ, Lightstone L, Clutterbuck EJ, Gaskin G, Pusey CD, Cook T, Warrens AN. Lesson of the week: cholesterol emboli syndrome. BMJ. 2000;321(7268):1065–7.
16. UK renal association clinical practice guideline on acute kidney injury. 2011. http://www.renal.org/guidelines/modules/acute-kidney-injury#sthash.MHcUy3ia.dpbs. Accessed 13 Jan 2014.
17. Cerdá J, Lameire N, Eggers P, Pannu N, Uchino S, Wang H, Bagga A, Levin A. Epidemiology of acute kidney injury. CJASN. 2008; 3(3):881–6.
18. Pereira BJ, Narang A, Pereira S, Gupta A, Sakhuja V, Chugh KS. Acute renal failure in infants in the tropics. Nephrol Dial Transplant. 1989;4(6):535–8.
19. Askenazi D. Evaluation and management of critically ill children with acute kidney injury. Curr Opin Pediatr. 2011;23(2):201–7.
20. Ganesan C, Maynard SE. Acute kidney injury in pregnancy: the thrombotic microangiopathies. J Nephrol. 2011;24(5):554–63. doi:10.5301/JN.2011.6250.
21. 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(5): 764–75. doi:10.5301/jn.5000058.
22. Coca SG, Cho KC, Hsu CY. Acute kidney injury in the elderly: predisposition to chronic kidney disease and vice versa. Nephron Clin Pract. 2011;119 Suppl 1:c19–24. Epub 2011 Aug 10.

23. Haase M, Story DA, Haase-Fielitz A. Renal injury in the elderly: diagnosis, biomarkers and prevention. Best Pract Res Clin Anaesthesiol. 2011;25(3):401–12.
24. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. N Engl J Med. 2009;361:62–72.
25. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine (Baltimore). 2005; 84(6):377–85.
26. Bagley WH, Yang H, Shah KH. Rhabdomyolysis. Intern Emerg Med. 2007;2(3):210–8.
27. Walsh S, Fan SL. Visualising rhabdomyolysis. Lancet. 2009;373(9658):154.
28. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis. 2002;39(5):930–6.
29. McCullough PA. Contrast-induced acute kidney injury. J Am Coll Cardiol. 2008;51(15):1419–28.
30. Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. Crit Care Med. 2008;36(4 Suppl):S216–23.
31. Costa S, Nucci M. Can we decrease amphotericin nephrotoxicity? Curr Opin Crit Care. 2001;7(6):379–83.
32. Denker B, Robles-Osorio ML, Sabath E. Recent advances in diagnosis and treatment of acute kidney injury in patients with cancer. Eur J Intern Med. 2011;22(4):348–54.
33. Humphreys BD, Soiffer RJ, Magee CC. Renal failure associated with cancer and its treatment: an update. J Am Soc Nephrol. 2005; 16:151–6.
34. Howard SC, Jones DP, Pui C-H. The tumor lysis syndrome. N Engl J Med. 2011;364:1844–54.
35. Barrantes F, Tian J, Vazquez R, et al. Acute kidney injury criteria predict outcomes of critically ill patients. Crit Care Med. 2008;36(5):1397–403.
36. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. Am J Med. 1983;74:243–8.
37. Shusterman N, Strom BL, Murray TG, Morrison G, West SL, Maislin G. Risk factors and outcome of hospital-acquired acute renal failure. Clinical epidemiologic study. Am J Med. 1987;83: 65–71.
38. Liaño F, Junco E, Pascual J, Madero R, Verde E. The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. Kidney Int. 1998;53:S16–24.
39. Cosentino F, Chaff C, Piedmonte M. Risk factors influencing survival in ICU acute renal failure. Nephrol Dial Transplant. 1994;9:179–82.
40. Lafrance J-P, Miller DR. Acute kidney injury associates with increased long-term mortality. J Am Soc Nephrol. 2010;21(2): 345–52.
41. Wald R, Quinn RR, Luo J, et al. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA. 2009;302(11):1179–85.
42. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81(5):442–8. doi:10.1038/ki.2011.379.