21.5 Acute kidney injury

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ESSENTIALS Definition—for practical clinical purposes, acute kidney injury (AKI) is defined as a significant decline in renal excretory function occurring over hours or days, detected by either a fall in urinary output or a rise in the serum concentration of creatinine. Oliguria—defined (ar- bitrarily) as a urinary volume of less than 400 ml/day—is usually pre- sent, but not always. Three stages of AKI are recognized, depending on the degree of the reduction in urinary output and/or the mag- nitude of the rise in serum creatinine, the latter now being widely used to trigger automated alerts from biochemistry laboratories to clinical staff. Epidemiology—the annual incidence of AKI in the United Kingdom population is about 0.6%, and AKI complicates 10 to 20% of medical and surgical admissions. Severe AKI (serum creatinine >500 μmol/ litre) affects 200 to 750 per million adult population per year in the United Kingdom. Clinical approach Diagnosis—all patients admitted to hospital with acute illness, but particularly older people and those with pre-existing chronic kidney disease, should be considered at risk of developing AKI. The most common precipitant is volume depletion, early detection of which requires careful monitoring of fluid input and output, lying and standing (or sitting) pulse and blood pressure, and daily weighing. Serum creatinine and electrolytes should be measured on admission in all acutely ill patients, and repeated daily or on alternate days in those who remain so. Assessment—after treatment of life-threatening complications, the initial assessment of a patient who appears to have AKI must an- swer three questions: (1) is the kidney injury really acute?—has serum creatinine been measured previously?; (2) is urinary obstruction a possibility?—renal ultrasonography is required urgently when the diagnosis of AKI is not clear cut (but remember that 5% of cases of obstruction will have a misleading initial ultrasound report); and (3) is there a renal inflammatory cause?—stick testing of the urine is man- datory in any patient with AKI, with urinary microscopy for cellular casts if this reveals significant proteinuria or haematuria. Red cell casts are found in acute glomerulonephritis, renal vasculitis, accelerated- phase hypertension, and (sometimes) in interstitial nephritis—their presence indicates the need for urgent specialist renal referral. General aspects of management The immediate management of a patient with renal impairment is directed towards three goals: (1) recognition and treatment of any life-threatening complications of AKI, (2) prompt diagnosis and treatment of hypovolaemia, and (3) specific treatment of the underlying condition—if this persists untreated then renal function will not improve. Life-threatening complications—the greatest danger is hyper kalaemia, which can cause cardiac arrest without any preceding symptoms whatsoever. All doctors who work with acutely ill pa- tients should be able to recognize the characteristic ECG ap- pearances, which are a better indicator of cardiac toxicity in the individual patient than the serum potassium level. As serum potas- sium rises, the following changes occur progressively: (1) 'tenting' of the T wave; (2) reduction in size of P waves, increase in the PR interval, widening of the QRS complex; (3) disappearance of the P wave, further widening of the QRS complex; (4) irregular 'sinus- oidal' ECG; and (5) asystole. Severe hyperkalaemic changes require immediate treatment with intravenous calcium (usually given as calcium gluconate, 10 ml of 10% solution, intravenously over 60 s), after which intravenous insulin/glucose or nebulized salbutamol can be used to reduce the serum potassium for a few hours to allow time for renal excretion (in cases of renal failure that are rap- idly treatable, e.g. bladder outflow obstruction) or initiation of renal replacement therapy. Fluid management—a key part of the immediate assessment and management of any patient who is very ill, which will include many of those with AKI, is to make a correct assessment of their intravascular volume status and to resuscitate rapidly and effect- ively, as discussed in Chapter 17.1. Once this has been achieved, in the patient who remains oliguric, fluid intake should be limited to the volume of the previous day's urine output and gastrointestinal losses, plus 500 ml, but this allocation may need to be substantially increased in the presence of fever or in hot environments, when insensible losses may be much increased. To keep the patient in the optimal state of fluid balance, there is no substitute for careful, twice-daily clinical examination for signs of intravascular volume depletion or excess, supplemented by accurate daily weighing, to gauge the overall net fluid balance, and an intelligent flexible re- sponse to the findings. 21.5 Acute kidney injury John D. Firth

section 21 Disorders of the kidney and urinary tract 4808 Renal replacement therapy—mandatory indications for immediate instigation are (1) refractory hyperkalaemia; (2) intractable fluid overload; (3) metabolic acidosis producing circulatory compromise; and (4) overt uraemia manifesting as encephalopathy, pericarditis, or uraemic bleeding. Modern practice is (whenever possible) to begin renal replacement therapy when the serum creatinine reaches 500 to 700 µmol/litre, unless there is clear evidence that spontan- eous recovery is occurring or there are other reasons to maintain a conservative approach. Renal biopsy—should be considered when (1) the history, examin- ation, or laboratory tests suggest a systemic disorder that could cause AKI and could be diagnosed by renal biopsy; (2) the urinary sediment contains red cell casts; (3) the case history is atypical; and (4) renal failure is unusually prolonged (say, beyond 6 weeks). Specific causes of acute kidney injury There are many possible causes of AKI, but in any given clinical con- text few of these are likely to require consideration. By far the most frequent are prerenal failure and acute tubular necrosis, which to- gether account for 80 to 90% of cases of AKI seen by physicians. Prerenal failure and acute tubular necrosis—these can best be re- garded as a continuum of renal response to ischaemic injury, in much the same way that stable angina, non-ST-elevation myocar- dial infarction, and ST-elevation myocardial infarction are a con- tinuum of cardiac response to ischaemia. Prerenal failure describes renal dysfunction that is entirely attributable to hypoperfusion, and where restoration of renal perfusion leads to rapid recovery. Acute tubular necrosis describes a clinical entity comprising AKI with three main characteristics: (1) it is seen in specific clinical contexts, fre- quently involving circulatory compromise and/or nephrotoxins; (2) urinary abnormalities usually suggest tubular dysfunction; and (3) recovery of renal function is expected within days or weeks, in most cases, if the patient survives the precipitating insult. There is no specific treatment for acute tubular necrosis, and it is a marker of severe illness with mortality around 15% in all cases, and 40 to 60% in series from intensive care units of patients receiving renal replacement therapy in the context of mechanical ventilation for respiratory failure. Introduction Definition For practical clinical purposes, acute kidney injury (AKI) has trad- itionally been defined as a significant decline in renal excretory function occurring over hours or days, detected by either a fall in urinary output or a rise in the serum concentration of creatinine. Oliguria—defined (arbitrarily) as a urinary volume of less than 400 ml/day—is usually present, but not always. The international guideline group, Kidney Disease: Improving Global Outcomes (KDIGO), has defined AKI more precisely as being any one of the following: • Increase in serum creatinine by greater than 0.3 mg/dl (>26 μmol/ litre) within 48 h • Increase in serum creatinine to greater than 1.5 times baseline level within 7 days (known or presumed) • Urinary output less than 0.5 ml/kg body weight per hour for 6 to 12 h AKI is then staged for severity according to criteria shown in Table 21.5.1, and the automated application of standard algorithms to measurements of serum creatinine performed in biochem- ical laboratories has led to the widespread practice of automated AKI alerts being sent to clinical staff (as now mandated by NHS England) in addition to the creatinine reading. Widespread agree- ment on the staging system for AKI has also been useful in sup- porting high-quality epidemiological studies, which have been important in showing that AKI is common, and also emphasizing that acute deterioration in renal function that leads to a small rise in serum creatinine is associated with poorer patient outcome: a little bit of kidney failure does matter. Epidemiology The application of automated alert systems has provided high- quality data on the epidemiology of AKI in patients in developed countries. In a large United Kingdom teaching hospital, from 2011 to 2013 the overall incidence of AKI in inpatients was 10.7%, with the highest stage being stage 1 in 7.2%, stage 2 in 2.2%, and stage 3 in 1.3% (with mortality 12.5%, 28.4%, and 35.7% respectively; overall 18.5%). Similar methodology applied prospectively to a population of three million in Wales (United Kingdom) in 2015 showed an incidence of AKI (of any stage) of 577 per 100 000 population, with community-acquired AKI accounting for 49% of episodes, and 42% occurring in the context of pre-existing chronic kidney disease. Ninety-day mortality was 25.6%. A 2011 United Kingdom population-based study reported the incidence of AKI requiring renal replacement therapy to be 184 per million popula- tion per year, which is very similar to the figure of 133 per million population per year reported in 2010 from Japan. Similar data are not available from resource-poor countries, but here the incidence of AKI is likely to be higher. Table 21.5.1 Stages of AKI AKI stage Urine output Serum creatinine 1 <0.5 ml/kg body weight per hour for 6-12 h Increase to 1.5–1.9 times baseline level within 7 days (known or presumed), or Increase by >0.3 mg/dl (>26 μmol/litre) within 48 h 2 <0.5 ml/kg body weight per hour for >12 h Increase to 2.0–2.9 times baseline level within 7 days (known or presumed) 3 <0.3 ml/kg body weight per hour for 24 h, or anuria for >12 h Increase to >3 times baseline level within 7 days (known or presumed), or Increase to >4 mg/dl (354 μmol/litre), or Initiation of renal replacement therapy Urinary obstruction must be excluded as a cause of low urine output. The most abnormal parameter—urine output, serum creatinine, or GFR—is used for classification.

21.5 Acute kidney injury 4809 A United Kingdom National Confidential Enquiry into Patient Outcome and Death (NCEPOD) of patients dying with a hospital- recorded diagnosis of AKI, published in 2009, examined the case notes and/or completed clinician questionnaires of 700 patients. This found an even split between men and women (48% vs 52%), and that most patients dying with AKI are elderly, with mean age 83 years (Fig. 21.5.1). Of the cases who had renal disease on admis- sion to hospital, 46% had a new diagnosis of AKI, 38% had acute on chronic renal failure, and 16% had chronic kidney disease (and developed additional AKI after admission). AKI developed before admission in 79% of patients and after admission in 21%. Causes AKI may arise as an isolated problem, but much more commonly occurs in the setting of circulatory disturbance associated with se- vere illness, trauma, or surgery, and in patients with many risk factors for AKI, most notably old age, medical comorbidities, medi- cations, previous chronic kidney disease, and hypovolaemia. There are many possible causes of AKI (Box 21.5.1), but in any given clinical context few of these are likely to require consideration. Table 21.5.2 shows the diagnoses made in 129 cases of acute renal impairment in 2216 consecutive medical and surgical admissions, and Table 21.5.3 shows the diagnoses established in 748 cases of AKI admitted to hospital in a prospective, multicentre, community- based study. Although these data are somewhat dated, they still re- flect current practice. The frequency of particular causes of AKI will vary considerably depending on the population studied. An observational cohort study of 618 patients in five American intensive care units found that over 70% of cases were due to or associated with ischaemic and/or nephrotoxic (radiocontrast media, rhabdomyolysis) acute tubular necrosis, prerenal failure, cardiac failure, or liver disease, and that the patients had extensive comorbidities (chronic kidney disease 30%, coronary artery disease 37%, diabetes mellitus 29%, and chronic liver disease 21%). Reports based on data from bio- chemical laboratories (including cases both admitted to hos- pital and managed in primary care) find that urinary obstruction (mainly prostatic) typically accounts for 25% or more of cases of acute impairment of renal function. Obstetric causes account for around 1% of cases of AKI in developed countries, but in some parts of the world up to 30%, and for obvious reasons snake bite is a common cause of AKI in some places, but exceptionally rare in others (see Chapter 21.11 for further discussion of renal disease in the tropics). 140 Number of patients 120 100 80 60 40 20 0 36 – 40 41 – 45 46 – 50 51– 55 56– 60 61– 65 66– 70 71– 75 76 – 80 Age (years) 81 – 85 86 – 90 91 – 95 96 – 100

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100 Fig. 21.5.1 Age distribution of 631 patients who died in hospitals in the United Kingdom with a diagnosis of AKI. Reproduced with permission from Stewart J, et al. (2009). Adding Insult to Injury. A review of the care of patients who died in hospital with a primary diagnosis of acute kidney injury (acute renal failure). National Confidential Enquiry into Patient Outcome and Death. http://www.ncepod.org.uk/2009aki.html Box 21.5.1 Some causes of acute kidney injury • Prerenal uraemia • ‘Acute tubular necrosis’—following haemodynamic compromise, com- monly with sepsis or following exposure to nephrotoxins, including drugs, chemicals, rhabdomyolysis, or snake bite (Table 21.5.7 and Box 21.5.3) • Vascular causes:

— Renal cortical necrosis

— Large-vessel occlusion

— Small-vessel occlusion—accelerated-phase hypertension and systemic sclerosis • Glomerulonephritis and vasculitis • Acute interstitial nephritis • ‘Haematological’ causes:

— Haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura

— Myeloma • Hepatorenal syndrome • Urinary obstruction:

— Intrarenal crystalluria

— Postrenal—renal stones, papillary necrosis, retroperitoneal fibrosis, bladder/prostate/cervical lesions, massive lymphadenopathy (lymphoproliferative disorders, secondary carcinoma)

section 21 Disorders of the kidney and urinary tract 4810 Clinical approach to patients with or at risk of acute kidney injury Diagnosis of the presence of acute kidney injury Symptoms and signs attributable to the accumulation of fluid, electro- lytes, acid, or uraemic wastes within the body are not apparent until AKI is far advanced, and the symptoms and signs that may arise are not specific: unsuspected hyperkalaemia is the greatest danger, since this may produce no symptoms whatsoever before causing cardiac arrest. All patients admitted to hospital with acute illness must therefore be considered at risk of developing AKI, and those who have pre-existing chronic kidney disease are particularly susceptible to acute exacerba- tions. This group includes all elderly patients, in whom a combination of low muscle mass and low dietary meat consumption may conspire to maintain an apparently ‘normal’ serum creatinine level, despite a reduction in glomerular filtration rate (GFR) to considerably less than 50% of that expected in a healthy young adult. For early recognition of AKI, the basic care of all acutely ill pa- tients should include careful monitoring of fluid input and output, lying and standing (or sitting) blood pressure, daily weighing, and regular estimation of serum creatinine and electrolytes. These blood tests should be performed on admission in all acutely ill patients, and repeated daily or on alternate days in those who remain so. If acted upon, these measurements will ensure that advanced AKI does not seem to have occurred ‘suddenly’ in patients already in hospital. Measurement of serum creatinine It is important to emphasize that a single measurement of serum cre- atinine cannot in isolation be used to determine the severity of acute renal impairment: if a patient with serum creatinine of 100 µmol/litre were to have both kidneys removed today, then the creatinine to- morrow would be only 150 to 200 µmol/litre. Clinical judgement, un- supported by measurement of serum creatinine, is a poor predictor of whether or not a patient has AKI, and patients who develop AKI after hospital admission not infrequently receive poor care. In the NCEPOD enquiry, the study’s advisors considered that 20% (22/107) of cases of AKI that developed after admission and which led to the patient’s death had been both predictable and avoidable. It is this, to- gether with other similar data, that has driven the introduction of the automated alert systems discussed previously, with the intention that these should support and stimulate clinicians to provide better care. Measurement of fluid input and output, and daily weighing Although it might seem to the inexperienced physician to be a simple matter to monitor fluid input and output, this is often not so in prac- tice, excepting in patients who are restricted to parenteral fluids and who have a urethral catheter. Drinks may be spilt, extra drinks may be acquired from a variety of sources, urine may be spilt, and vomit and diarrhoea are often found in places where they are difficult to quantitate. These considerations mean that the most likely explan- ation for fluid balance charts being difficult to interpret is the erro- neous recording of input or output. Daily weighing on accurate scales provides a much more reliable picture of net overall fluid balance. Patients who are acutely ill in- variably lose flesh weight, commonly at a rate of up to a few hundred grams per day. If weight appears to fall at a rate faster than this, then negative fluid balance is the reason, with the occurrence of greatly increased ‘insensible’ losses through the skin and lungs during fever being a common explanation. Physical signs Aside from weight loss, the most reliable physical signs of significant intravascular volume depletion are the development of postural diz- ziness, a postural rise in pulse rate (>30 beats/min), and the finding Table 21.5.2 Causes of development of acute impairment of renal function in 2216 consecutive medical and surgical admissions Cause Number of patients Acute tubular necrosis: Hypovolaemia 22 Congestive cardiac failure 10 Sepsis 10 Nephrotoxins 25 Postsurgical 23 Other 12 Hepatorenal syndromea 5 Obstruction 3 Vasculitis 2 Other/multifactorial/unknown 17 Total 129 (5.8% of admissions) Acute impairment of renal function was diagnosed when the serum creatinine concentration rose by a predetermined amount (approximately one-third of the baseline) during the period of hospital admission. During the period of study, 46 patients were excluded from analysis because they were either admitted specifically for treatment of acute renal failure or were recipients of long-term haemodialysis. Dialysis was required in 10 cases. a The frequency of hepatorenal syndrome was higher in this study than in routine clinical practice in most centres, presumably as a reflection of referral bias. Modified from The American Journal of Medicine 74;2;6, Hospital-acquired renal insufficiency: A prospective study, Hou, Bushinsky, Wish, Cohen & Harrington © 1983, with permission from Elsevier. Table 21.5.3 Causes of acute kidney injury established in all cases (748) admitted to 13 tertiary-care hospitals in Madrid, Spain, over a 9-month period Cause Proportion of patients (%) Acute tubular necrosis 45 Prerenal 21 Acute-on-chronic kidney disease 13 Urinary tract obstruction 10 Glomerulonephritis or vasculitis 4 Acute interstitial nephritis 2 Atheroemboli 1 AKI was diagnosed when a sudden rise in serum creatinine to >177 μmol/litre was found in patients with previously normal renal function, or when there was a sudden rise of

> 50% in those known to have mild to moderate chronic renal failure. Most cases of acute-on-chronic kidney disease were due to prerenal cause or acute tubular necrosis, and most cases of obstruction were due to prostatic disease in elderly men. Dialysis was required in 36% of cases. Modified from Liano F, Pascual J. (1996). Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. Kidney Int, 50, 811–18, with permission.

21.5 Acute kidney injury 4811 of dry axillae. If weight rises at any time, then this must be due to positive fluid balance, whatever the input/output charts may sug- gest. It may not be obvious from clinical examination where the fluid has gone: the possibilities of sequestration in the peritoneal cavity or in the tissue interstitium should be recognized. Prevention of acute kidney injury Many patients develop AKI while in hospital, which can occur despite exemplary care but is more likely if care is deficient. The NCEPOD report into the deaths of over 1000 patients with AKI found that good care (defined as that which you would accept from yourself, your trainees, and your institution) was provided in only 50% of cases, and that in many instances the development of AKI had been both predictable and avoidable. Given that patients who develop AKI are admitted under many specialties, and very few by nephrologists (Fig. 21.5.2), it is im- portant that all doctors caring for sick patients understand those who are at particular risk of developing AKI and implement meas- ures that will reduce the likelihood of this occurring and respond in an appropriate and timely manner if it does. Risk factors and care bundles Risk factors for AKI are shown in Table 21.5.4. Appropriate re- sponses to the development of AKI can be articulated in the form (to use currently fashionable jargon) of a ‘care bundle’ (Table 21.5.5), and guidance disseminated (Fig. 21.5.3). Key elements of this are prompt recognition and treatment of sepsis, optimization of fluid volume status, and avoidance of toxins. Antihypertensives, with the possible exception of β-blockers when these are prescribed for is- chaemic heart disease, should be stopped if blood pressure is low. A meta-analysis of randomized controlled trials has shown that stopping angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) before coronary angiography or coronary surgery reduces the risk of AKI. There is no such trial evidence for stopping these drugs during intercurrent illness in pri- mary or secondary care, but a longitudinal ecological study sug- gested that up to 15% of the increase in AKI admissions in England over a four-year time period was potentially attributable to increased prescribing of ACE inhibitors and ARBs. It would therefore widely be regarded as good practice to advise patients to temporarily dis- continue these drugs in the presence of illnesses causing fluid loss (e.g. vomiting, diarrhoea, and high fever) or evidence of volume de- pletion (e.g. postural dizziness or light-headedness, reduced home- measured blood pressure). Glycaemic control Critical illness is associated with stress hyperglycaemia, and in a range of circumstances a linear relationship between blood glucose levels and adverse clinical outcomes has been shown. It has also been shown that maintaining tight glycaemic control by intensive insulin therapy can improve outcomes, including reducing the incidence of severe AKI in both medical and surgical intensive care unit pa- tients. KDIGO recommendations are that the average blood glucose should not be allowed to exceed 150 mg/dl (8.3 mmol/litre), but 200 Number of patients 180 160 140 120 100 80 60 40 20 0 Admitting specialty General medicine Care of the elderly Thoracic medicine Gastroenterology Cardiology Endocrinology Nephrology General surgery Diabetic medicine Urology Haematology Trauma & Orthopaedics Critical care medicine Upper GI surgery Vascular surgery Fig. 21.5.2 Admitting specialty of 631 patients who died in hospitals in the United Kingdom with a diagnosis of AKI. Reproduced with permission from Stewart J, et al. (2009). Adding Insult to Injury. A review of the care of patients who died in hospital with a primary diagnosis of acute kidney injury (acute renal failure). National Confidential Enquiry into Patient Outcome and Death. http://www.ncepod.org.uk/2009aki.html

section 21 Disorders of the kidney and urinary tract 4812 Table 21.5.5 A care bundle approach to assessment and management of patients who have developed AKI Initial assessment ABCDE assessment Vital signs—check NEWS score Look for signs of sepsis Physical exam for large bladder (bedside bladder scan) Medication review Stop potentially harmful drugs; check if dose adjustments required in renal impairment Initial management Give fluid challenge if hypovolaemic/hypotensive Prompt treatment of sepsis Relieve bladder outflow obstruction if present Stop potentially harmful drugs (NSAIDs, ACE inhibitors, ARBs, diuretics) Check if medications require dose adjustments in renal impairment Maintain glycaemic control Indications for immediate referral for specialty input Renal—complications of AKI refractory to medical treatment (most notably hyperkalaemia or pulmonary oedema as indications for dialysis); likely intrinsic renal disease/systemic vasculitis; special circumstances (e.g. renal transplant patient) Radiology and/or urology—bladder outflow obstruction that cannot be relieved by urinary catheter passed by admitting team; obstructed and infected kidney (pyonephrosis) Critical care—haemodynamic instability; multiorgan failure Further investigation Urinalysis—significant haematuria and proteinuria indicate need for immediate renal referral in context of AKI Cultures for sepsis Venous lactate and arterial blood gases (if sepsis or high NEWS score) Imaging with ultrasonography within 24 h to look for obstruction unless AKI improving or other diagnosis established Other tests based on clinical suspicion (see text) Ongoing monitoring Fluid balance charts, daily weights Daily clinical assessment, with particular attention to volume status Daily

review of medication charts Regular blood tests (creatinine, electrolytes, glucose) Nutritional assessment Specialty referral within
24 hours Renal—AKI that is not starting to recover Radiology and/or urology—obstruction on ultrasonography not relieved by urinary catheter, or persistent clinical suspicion of obstruction as underlying diagnosis ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs. Source data from 'Recommended minimum requirements of a care bundle for patients with AKI in hospital', published December 2015, www.thinkkidneys.nhs.uk. Copyright © 2018 Think Kidneys, NHS England, UK Renal Registry. Table 21.5.4 Risk factors for AKI in patients admitted to hospital Nonmodifiable risk factors Comment Modifiable risk factors Comment Age >75 years Hypovolaemia Chronic kidney disease eGFR <60 ml/min Drugs with adverse renal haemodynamic effects in acute illness NSAIDs ACE inhibitors ARBs Diuretics History of AKI Nephrotoxic drugs Aminoglycosides Iodinated radiological contrast agents Diabetes mellitus Sepsis Cardiac failure Glycaemic control Vascular disease Liver disease Cognitive or neurological impairment or disability May limit access to fluids without assistance ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.

21.5 Acute kidney injury 4813 that (because of the risk of inducing serious hypoglycaemia) insulin therapy should not be used to reduce the blood glucose to below 110 mg/dl (6.1 mmol/litre). Maintaining control within these limits is challenging and, unless the circumstances are such that very close monitoring of blood glucose can be assured 24/7, it is safer for a patient's blood glucose to be too high rather than too low. Diagnosis of the cause of acute kidney injury The physician must try to make a precise diagnosis of the cause of AKI in all cases. After treatment of life-threatening complications (see later), the initial assessment of a patient who appears to have AKI must answer three questions. Question 1: is the kidney injury really acute? The only basis for excluding the possibility of pre-existing chronic kidney disease with absolute confidence is the knowledge of a pre- vious normal measurement of renal function. In cases where there is uncertainty, a diligent search for previous notes and biochemical information may save the patient and the doctor the inconvenience (and occasionally hazard) of unnecessary investigation. The finding of two small kidneys on ultrasound examination indicates the pres- ence of chronic kidney disease. Other clinical features are poor dis- criminators between acute and chronic renal impairment. A history of vague ill health of some months duration, of nocturia, of pruritus, or the findings of skin pigmentation or anaemia, would all suggest chronicity (see Chapters 21.3 and 21.6). However, anaemia is not in- variable in advanced chronic kidney disease (e.g. in polycystic kidney disease the haemoglobin concentration may be normal), and an- aemia can develop over a few days in AKI, as may hypocalcaemia and hyperphosphataemia. Radiological evidence of renal osteodystrophy is only found in patients with obviously long-standing renal failure. Question 2: is urinary obstruction a possibility? One of the merits of the traditional division of the causes of AKI into prerenal, renal, and postrenal is that it encourages consideration of the possibility of urinary obstruction. It is extremely important that obstruction should not be missed, since most cases are readily treat- able and delayed diagnosis may lead to permanent renal damage. Obstruction is particularly likely to cause AKI in those with a single functioning kidney, in those with a history of renal stones or of Fig. 21.5.3 AKI risk and prevention guidance for secondary care. To the best of our knowledge, the contents of this publication are in line with National Institute for Health and Care Excellence guidance relating to the management and treatment of acute kidney injury. Professional advice should be sought before taking, or refraining from taking, any action on the basis of the content of section 21 Disorders of the kidney and urinary tract 4814 prostatism, and after pelvic or retroperitoneal surgery, but the possi- bility of obstruction should be seriously considered in all cases where another positive diagnosis cannot be made. The presence of anuria, or of alternating polyuria and oligoanuria, are helpful clues. However, it is not widely appreciated that a patient may pass normal or elevated volumes of urine despite significant obstruction, although this is ex- tremely rare. The mechanism is poorly understood, but three factors present in obstruction tend to impair urinary concentrating ability, thereby leading to the preservation of urinary volume despite ob- structive depression of the filtration rate. These factors are structural damage to the inner medulla and papilla, functional changes in the distal nephron resulting from increased intraluminal or interstitial pressure, and loss of medullary hypertonicity at low filtration rates. Ultrasound examination of the kidneys and bladder is the usual first method of investigation for the presence of obstruction (Fig. 21.5.4). However, it is important to remember that the quality of the image obtained by renal ultrasonography is highly vari- able, depending on the patient, the equipment, and the operator. Furthermore, ultrasonography detects pelvicalyceal dilatation, not obstruction, and the test may be ‘negative’ (because the renal pelvis and calyces fail to dilate, or do so only minimally) in about 5% of cases of acute obstructive renal failure. If, following ultrasound examination, doubt as to the diagnosis of obstruction persists in the clinician’s mind, then the usual next step will be to request CT scanning of the abdomen and pelvis, which generally gives better anatomical definition. If the question is whether or not a dilated renal collecting system, demonstrated by either ultrasonography or CT scanning, is due to functional ob- struction or to a ‘baggy’ renal pelvicalyceal system, then—if renal function is adequate (creatinine concentration less than about 250 μmol/litre)—diethylenetriaminepentaacetic acid (DTPA) or mercaptoacetyltriglycine (MAG3) renography with furosemide in- jection may be helpful, showing delayed excretion and clearance of radionuclide from the obstructed kidney(s). If renal function is severely impaired then imaging modalities that depend on renal excretion (including intravenous pyelography) are not useful, and percutaneous antegrade nephrostomy/pyelography or cystoscopy with retrograde ureteric catheterization and pyelography should be undertaken. (See Chapters 21.4 and 21.17 for further discussion.) Obstruction, once diagnosed, must be relieved urgently by (as possible and appropriate) insertion of a urethral or suprapubic cath- eter, antegrade percutaneous nephrostomy, or cystoscopic inser- tion of ureteral stents, as a prelude to definitive treatment (where possible) of the underlying obstructive lesion. The most important causes of urinary obstruction are renal calculi, retroperitoneal fi- brosis, and malignant diseases of the uterine cervix, prostate, bladder, and rectum (see Chapter 21.17). Question 3: is there a renal inflammatory cause? Renal inflammatory conditions—including glomerulonephritis, interstitial nephritis, vasculitis, and other rarities—together account for fewer than 10% of cases of AKI. To make these diagnoses, which have critically important management implications, stick testing of the urine and microscopy of the urinary sediment is an essential part of the assessment of any patient with unexplained acute renal impairment. If stick testing indicates more than ‘+’ of protein or more than a trace of blood, then a sample of urine should be examined under the micro- scope. This should be done by centrifuging 10 to 15 ml of urine at 1500 to 2500 rev/min (c.400–1120 g) for 5 min, carefully discarding all but 1 ml of the supernatant, and then resuspending the pellet. Examination should be made under high power, preferably after staining, which makes the cellular elements of casts more obvious. Urinary casts containing red blood cells (Fig. 21.5.5) are present in acute glomer- ulonephritis, renal vasculitis, accelerated-phase hypertension, and (sometimes) in interstitial nephritis, but not in other conditions. Their presence indicates the need for urgent specialist renal referral. Clinical features of acute kidney injury The early stages of AKI do not produce any obvious clinical features, and—as stated previously but worthy of emphasis—the main clin- ical risk is of hyperkalaemic cardiac arrest arising (apparently) out of the blue. Most patients who are unwell do not drink as much as usual and therefore pass less urine than normal, hence enquiry along the lines of 'Are you passing less urine than normal?' is rarely illuminating. Furthermore, as many as 50% of cases of AKI are not oliguric. The clinical picture is likely to be dominated by the primary condition of which AKI is a complication, and by the effects of intravascular volume depletion, with dizziness caused by postural hypotension a common reason for patients being brought to medical attention. Fig. 21.5.5 A cellular urinary cast. ∗ ∗ Fig. 21.5.4 Ultrasound image of an obstructed left kidney, showing pelvicalyceal dilatation (asterisks). The horizontal dotted line measures the length of the kidney (normal in this case), and the renal cortex is well preserved (not a thin rim), both of which suggest that there is a high likelihood that function will recover substantially when obstruction is relieved.

21.5 Acute kidney injury 4815 In the later stages of AKI there are manifestations of uraemia with anorexia, nausea, vomiting (or occasionally diarrhoea), mus- cular cramps, and signs of encephalopathy—including a 'meta- bolic' flapping tremor (asterixis), progressing in extreme cases to depressed consciousness and grand mal convulsions. Skin bruising and gastrointestinal bleeding may occur. Uraemic haemorrhagic pericarditis is another potentially fatal complication, but this oc- curs much less frequently in AKI than in (neglected) chronic renal failure. For further discussion see Chapter 21.3. Biochemical changes The diagnosis of renal impairment, acute or chronic, is made when the serum urea and creatinine concentrations rise. Other important biochemical changes include the development of hyperkalaemia, metabolic acidosis, hypocalcaemia, and hyperphosphataemia. Hyperkalaemia is due not only to reduced urinary excretion, but also to potassium release from cells—either as a consequence of cell death or as a result of metabolic acidosis. Particularly rapid rises are to be ex- pected when there is extensive tissue damage or hypercatabolism, as in rhabdomyolysis, burns, and sepsis. Transfusion of stored blood is sometimes said to cause dangerous rises in serum potassium concen- tration in oliguric patients. However, the transfused blood may not really be to blame, but the circumstances that demand transfusion. Loss of blood into the gastrointestinal tract or body tissues is followed by red cell lysis and the absorption of a considerable potassium load. Protein catabolism produces sulphuric and phosphoric acids. These are normally buffered by bicarbonate and excreted by the kidney. In AKI these systems fail, leading to the development of acidosis. This is usually modest in degree (plasma pH 7.2–7.35), but can be more severe, manifesting as sighing Kussmaul's respiration and/or circulatory compromise. Acidosis is rarely the metabolic ab- normality most obviously necessitating urgent institution of renal replacement therapy, but overzealous administration of bicarbonate should be avoided (see following paragraph). Calcium malabsorption occurs early in AKI and is probably sec- ondary to disordered vitamin D metabolism. Hypocalcaemia can develop with surprising rapidity. It is usually asymptomatic, but tetany and fits may be provoked by injudicious over-rapid correction of acidosis with resultant depression of ionized calcium. Profound hypocalcaemia and marked hyperphosphataemia, together with hyperuricaemia, is to be expected in rhabdomyolysis. Transient hypercalcaemia is frequently seen during the recovery phase from AKI, and this is particularly common after rhabdomyolysis, prob- ably being caused by secondary hyperparathyroidism related to pre- ceding hypocalcaemia. The hypercalcaemic phase may be prolonged and accompanied by metastatic calcification in patients in whom there has been extensive muscle injury. The serum sodium concentration is usually normal in cases of AKI: any deficit of sodium is usually matched by that of water, thus leading to reduction of the extracellular fluid volume but with an unchanged serum sodium concentration. However, on occasion the intake of water, either drunk in response to thirst or inflicted iatrogenically (typically by 5% dextrose infusion), may exceed the rate of excretion such that hyponatraemia results. The retention of uric acid, sulphate, and magnesium occurs in renal failure, but these biochemical abnormalities are rarely clinically significant, with the exception of the grossly elevated levels of uric acid that can be seen in rhabdomyolysis and following tumour lysis. General aspects of acute kidney injury The immediate management of patients with renal impairment is directed towards three goals. The first is the recognition and treat- ment of any life-threatening complications of AKI. The second is prompt diagnosis and treatment of hypovolaemia. The third is spe- cific treatment of the underlying condition: if this persists untreated then renal function will not improve. Life-threatening complications Hyperkalaemia Hyperkalaemia, which is rarely a significant clinical problem in pa- tients who do not have renal failure, is important in the context of AKI or chronic kidney disease because it can cause cardiac arrest. Patients may occasionally notice muscle weakness or paralysis, but the significance of these symptoms is rarely appreciated, and usu- ally there are no symptoms whatsoever. All doctors who work with acutely ill patients should be able to recognize the characteristic ECG appearances, which are a better indicator of cardiac toxicity in the individual patient than the serum potassium level. As serum po- tassium rises, the following changes occur progressively: 1. ‘Tenting’ of the T wave 2. Reduction in size of P waves, increase in the P–R interval, widening of the QRS complex 3. Disappearance of the P wave, further widening of the QRS complex 4. Irregular ‘sinusoidal’ ECG (Fig. 21.5.6) 5. Asystole Standard definitions are that a serum potassium concentration of 5.5 to 5.9 mmol/litre is described as mild hyperkalaemia, 6.0 to 6.4 mmol/litre as moderate, and greater than 6.5 mmol/litre as severe. Treatment of hyperkalaemia is described in Table 21.5.6, but in determining whether treatment is required, and what that treat- ment should be, it is important to understand the clinical context. It is acute rises in serum potassium that cause cardiac arrest, and la- boratory notification of a serum potassium result of (say) 6.5 mmol/ litre in a routine blood sample taken in primary care or outpatient practice for monitoring of a patient who is not acutely unwell should not, on the grounds that it is ‘severe’, automatically precipitate a rec- ommendation for hospital admission and management with intra-venous calcium and/or insulin and dextrose. Many patients with chronic kidney disease have a serum potassium concentration in the range 6.1 to 6.5 mmol/litre, or even a bit higher (particularly if they are taking ACE inhibitors or ARBs, or have hyporeninaemic hypoaldosteronism, which is most common in those with dia- betes or chronic interstitial renal disease), which they tolerate well, without any significant ECG changes. The appropriate clinical re- sponse in this circumstance is to advise discontinuation of any drug that will exacerbate hyperkalaemia (including ACE inhibitors and ARBs), institution of a low potassium diet (see Table 21.2.2.3), and repeat measurement in a few days’ time. Various drugs can reduce serum potassium by increasing elimination of potassium from the gut. Calcium resonium and patiromer release calcium ions in ex-change for potassium; zirconium cyclosilicate selectively captures potassium ions. Calcium resonium is not suitable for administra- tion for more than a few days because it is unpalatable and causes

section 21 Disorders of the kidney and urinary tract 4816 severe constipation, sometimes to the point of faecal perforation, and the proper uses of patiromer and zirconium cyclosilicate are not yet established. Many physicians will rightly regard giving a drug to counteract the side effect of another drug (one which causes hyperkalaemia) as intuitively unattractive, and doing so will clearly compound hazards of polypharmacy. Pulmonary oedema The most serious complication of salt and water overload in AKI is the development of pulmonary oedema, which is usually iatrogenic, being caused by continued ill-advised intravenous in- fusion of fluids into patients who are anuric or oliguric. Severe cases are dramatic. The patient is terrified, restless, and confused. Examination reveals cyanosis, tachypnoea, tachycardia, wide- spread wheeze or crepitations in the chest, and a gallop rhythm (if the heart can be heard). Investigation demonstrates arterial hyp- oxaemia and widespread interstitial shadowing on the chest radio- graph. (See Chapter 16.5.2 for further discussion.) The patient should be sat up and supported, and given oxygen by facemask in as high a concentration as possible using a reservoir Table 21.5.6 Treatment of hyperkalaemia Treatment Comment 1 Intravenous calcium (10 ml of 10% calcium chloride or gluconate, over 60 s, repeated until ECG improves) Treatment to be given immediately if hyperkalaemia is associated with ECG changes more severe than tenting of the T wave. Acts instantly to 'stabilize' cardiac membranes (mechanism unknown). Does not alter serum potassium concentration 2 Intravenous insulin and glucose (10 units of rapidly acting insulin plus 50 ml of 50% dextrose, over 10 min) Insulin stimulates Na^+,K^+-ATPase in muscle and liver, thus driving potassium into cells. Serum potassium falls by 1–2 mmol/litre over 30–60 min. Blood glucose concentration should be monitored at regular intervals for a minimum of 6 h after administration of insulin-dextrose
(danger of hypoglycaemia) 3 Nebulized salbutamol (10–20 mg) β2-agonists stimulate Na^+,K^+-ATPase in muscle and liver, thus driving potassium into cells. Serum potassium falls by 1–2 mmol/litre over 30–60 min. Induces tremor and tachycardia, and sometimes nausea and vomiting 4 Intravenous sodium bicarbonate (50–100 ml of a 4.2% solution, over 10 min) Traditionally thought to act by increasing blood pH, inducing exchange of intracellular protons for extracellular potassium. May not work in this manner since hypertonic saline has been shown to be effective. Only to be used if there is severe acidosis that merits treatment in its own right, and should not be used routinely in the management of hyperkalaemia. Glucose/insulin and salbutamol are equally effective and do not have the disadvantages of (1) requiring a large sodium load, (2) being severe chemical irritants ('burns' requiring surgical debridement and reconstruction can occur if concentrated bicarbonate gets into tissues from peripheral intravenous lines), and (3) carrying a risk of precipitating severe hypocalcaemia 5 Cation exchange resins, e.g. sodium or calcium polystyrene sulphonate (15 g by mouth every 6 h or 15–30 g per rectum every 6 h), or other oral agents that increase excretion of potassium from the gastrointestinal tract Exchange sodium or calcium for potassium in the gut lumen and thus induce loss of potassium from the body (unlike 1–3 above in table). Take 4 h to produce an effect and are not to be used in the emergency treatment of severe hyperkalaemia. 6 Haemodialysis/filtration Except in those rare cases where renal function can be rapidly restored (e.g. relief of obstruction), it is likely that hyperkalaemia will recur and haemodialysis or high-volume haemofiltration will be required Treatment with insulin/glucose and with β2-agonists works in the same way, hence their effects in reducing serum potassium are not additive and there is no benefit in giving both together. The side effects of β2-agonist treatment mean that insulin/glucose is to be preferred if it can be administered easily.
Fig. 21.5.6 An ECG showing severe hyperkalaemic changes in a patient with a serum potassium level of 9.4 mmol/litre.

21.5 Acute kidney injury 4817 bag. Furosemide may work as a venodilator but is unlikely to provoke a substantial diuresis in a patient with renal failure. Morphine can relieve symptoms rapidly and should be given (along with an antiemetic) in small (2.5–5 mg) doses, repeated if necessary and if tolerated, and with the opioid antagonist naloxone to hand in the event of respiratory depression. An intravenous infusion of a venodilator such as isosorbide dinitrate may be helpful. Continuous positive airway pressure or noninvasive positive pressure ventilation can be very useful in supporting the patient until such time as fluid can be removed, the definitive treatment for pulmonary oedema caused by renal failure being haemodialysis or haemofiltration. Acute peritoneal dialysis is much less effective in this capacity and should only be considered in circumstances where haemodialysis and haemofiltration are not available. The immediate beneficial ef- fects of venesection of 200 to 400 ml of blood from the patient in extremis should not be forgotten. Recognition and treatment of volume depletion A key part of the immediate assessment and management of any patient who is very ill, which will include many of those with AKI, is to make a correct assessment of their intravascular volume status and to resuscitate rapidly and effectively. The NCEPOD report dis- cussed earlier in this chapter identified that a common failing was that hypovolaemia was not recognized and treated appropriately. Fluid and electrolyte requirements in established

acute kidney injury Fluid Many patients with AKI are volume depleted at the time of presen- tation. An urgent priority is to correct such depletion rapidly. Once this has been achieved—as judged by an improvement in peripheral perfusion, a fall in pulse rate, loss of postural drop in blood pressure, and a rise in jugular venous pressure—the perspective changes. In the absence of normal renal function, the greatest care must be taken to regulate the intake of fluids and electrolytes to match losses in the urine, from the gastrointestinal tract, and from other ‘insens- ible’ sources. As a working rule, fluid intake is limited to the volume of the previous day’s urine output and gastrointestinal losses, plus 500 ml, but this allocation may need to be substantially increased in the presence of fever or in hot environments, when insensible losses may be much increased. However, as discussed previously, fluid- balance charts are frequently inaccurate, hence unthinking adher- ence to the ‘output plus 500 ml’ rule can lead to grief. To keep the patient in the optimal state of fluid balance, there is no substitute for careful, twice-daily clinical examination for signs of intravas- cular volume depletion or excess, supplemented by accurate daily weighing to gauge the overall net fluid balance, and an intelligent flexible response to the findings. Sodium In patients who are not being dialysed, the intake of sodium must also be matched to output. Requirements are usually very small in those who are oliguric, perhaps only 15 to 30 mmol/day, but if the patient is polyuric the requirements can be considerable, with a danger of volume depletion if these are not met. The urine of a pa- tient with polyuric renal failure will usually contain sodium at a concentration of 50 to 70 mmol/litre; hence, if urine output is 3 litres/ day then over 200 mmol of sodium may be required. On occasion, the urine output in polyuric AKI can be massive (even up to 1 litre/ h), and if the response is to administer an even greater quantity of fluid (output plus insensible losses), then it is possible to contrive a vicious cycle whereby an ever-increasing urinary output is rewarded by ever-increasing fluid infusion. To avoid this situation in a patient with polyuria, it is best to limit input to urinary output alone, thus al- lowing other fluid losses to establish a mild overall negative balance, only increasing fluid input if the patient develops significant pos- tural hypotension, which should be checked for twice daily. For un- known reasons, an excess of sodium and water in patients with acute tubular necrosis leads to peripheral or pulmonary oedema, whereas in those with glomerulonephritis it tends to produce hypertension. Potassium Because hyperkalaemia is one of the most important problems in the management of patients with AKI, it is essential to check serum potassium levels at least daily, and in those with hypercatabolism or gastrointestinal bleeding, or who require surgery, more frequent estimations are advisable. In oliguric cases, dietary consumption should be limited to the minimum compatible with an adequate in- take of protein and amino acids (20–30 mmol/day). Diuretics that work on the distal tubule (e.g. spironolactone, amiloride, and triamterene) promote potassium retention and should be stopped in all patients with AKI, and it is important when reviewing the drug chart to remember that these agents are frequent constituents of tablets containing a combination of di- uretic/antihypertensive compounds. ACE inhibitors and ARBs similarly increase serum potassium and should be stopped, as discussed previously. Intravenous preparations of antimicrobial agents that contain large amounts of potassium should also be avoided whenever possible. Excretion of potassium can sometimes be enhanced in those who are oliguric by the use of high doses of furosemide (0.5–1 g daily). Oral potassium-exchange resins (e.g. polystyrene sulphonate resins, prescribed concurrently with a laxative to avoid very severe consti- pation, even faecal perforation), can be useful in controlling serum potassium for a few days or weeks, but they and other oral agents are not effective treatments for acute severe hyperkalaemia (see Table 21.5.6). By contrast, substantial losses of potassium can occur in polyuric AKI and need to be replaced. Measurement of the urinary potas- sium concentration can be helpful in estimating how much potas- sium is required in this circumstance. Renal replacement therapy Mandatory indications for immediate instigation of renal replace- ment therapy are: • refractory hyperkalaemia • intractable fluid overload • metabolic acidosis producing circulatory compromise • overt uraemia manifesting as encephalopathy, pericarditis, or uraemic bleeding These indications will be present in some patients on their admis- sion to hospital, but in many cases renal function will decline over a period of days or a few weeks when the patient is under observation in hospital, and the literature gives no clear message as to when renal replacement therapy should be initiated. There is no level of nitro- genous waste at which the patient suddenly becomes susceptible to overt uraemic sequelae. Nevertheless, it is clearly not sensible to wait

 until an obvious uraemic complication (which might be fatal) arises. Some studies have reported better outcomes in patients who were started on renal replacement therapy earlier rather than later, but others have not, and much of the evidence is of low quality. In the ab- sence of an indication such as hyperkalaemia, fluid overload, or se- vere acidosis, modern practice is (whenever possible) to begin renal replacement therapy when the blood urea reaches 25 to 35 mmol/ litre and the serum creatinine 500 to 700 µmol/litre, unless there is clear evidence that spontaneous recovery is occurring or other reasons to maintain a conservative approach. There are three basic options for renal replacement therapy: peritoneal dialysis, haemodi- alysis, and haemofiltration. Peritoneal dialysis Peritoneal dialysis is technically the simplest form of renal replace- ment therapy and available in some settings where haemodialysis or haemofiltration is not. Little has been published recently about its use in patients with AKI, but a systematic review in 2017 of six studies with 484 participants concluded that there was probably little or no differ- ence in outcomes produced by peritoneal dialysis or extracorporeal therapy. The principle is the same as that described for the long-term treatment of patients with chronic renal failure (see Chapter 21.7.2), the main differences being that (1) catheters are used which can be inserted percutaneously using a metal stylet (although some use the same type of catheter as that used for continuous ambulatory treat- ment), and (2) smaller volume exchanges with shorter dwell times are the norm. Details of how to make up fluid suitable for performing peritoneal dialysis from intravenous fluids can be found at https://

ispd.org/ispd-guidelines/. The technique requires an intact peri- toneum and is therefore precluded in the many patients whose renal failure is associated with abdominal surgery. Other problems include difficulties in maintaining dialysate flow, leakage, peritoneal infection, protein losses, and restricted ability to clear fluid and uraemic wastes. Notwithstanding the systematic review reported just mentioned, it is fair to say that peritoneal dialysis is virtually never the first-choice mo- dality for renal replacement therapy in an adult with AKI in centres that have a range of techniques at their disposal. Haemodialysis and haemofiltration Haemodialysis is an intermittent technique, usually applied three times per week in the context of chronic renal failure (see Chapter 21.7.1), but often used more frequently (up to every day) in the management of patients with AKI. By contrast, haemofiltration is a continuous technique, brief details of which are as follows: a mechanical pump (but sometimes the patient's own arterial pres- sure) drives blood through a haemofilter of high hydraulic con- ductivity. An ultrafiltrate of plasma is removed, usually at a rate of between 1 and 2 litre/h. This is replaced, minus the volume of other fluid inputs and the amount of 'negative balance' required, using (most commonly) a lactate/acetate-based substitution fluid. A large number of technical variations are possible—for example, a com- bination of filtration and dialysis elements (haemodiafiltration), and use of differing replacement fluids—but there is nothing to suggest that any one of these is better than another, excepting in those who are unable to metabolize lactate, when bicarbonate-based substitu- tion fluid is essential. Theoretical advantages of haemofiltration over haemodialysis in the management of patients with AKI include enhanced haemo- dynamic stability, increased ability to remove salt and water (allowing better prevention of volume overload and permitting im- proved nutrition), and greater clearance of inflammatory mediators (which may provide advantage in patients with sepsis). However, meta-analyses of trials that have compared intermittent with con- tinuous treatments in the context of AKI have not shown important differences in outcomes, and usage depends on local custom and practice. In the same way that there is no evidence on which to make firm recommendations as to when to start renal replacement therapy in those with AKI whose chemistry is gradually 'going off', there is also little information on which to base targets for the clearance of metabolic wastes that should be achieved by treatment. For inter- mittent or extended (sustained low efficiency dialysis, where treat- ment typically takes 8 h compared to the usual 3–4 h for a standard dialysis treatment) renal replacement therapy, KDIGO guidelines recommend delivering a Kt/V greater than 3.9 per week. Most trials of daily haemodialysis versus thrice-weekly haemodialysis have not shown advantage of daily treatment, provided that an adequate dialysis dose (Kt/V >1.2) is delivered thrice weekly. With regard to continuous treatments, the standard of care is to provide an effluent (filtrate/dialysate) flow rate of 20 to 25 ml/kg body weight per hour, and exceeding this provides no clearly proven benefit. Other issues in the management of patients

with acute kidney injury Indications for renal biopsy Most cases of AKI are due to prerenal failure or to the clinical syn- drome of acute tubular necrosis. They occur in an appropriate clin- ical setting and follow a typical time course, with recovery of renal function over a few weeks. In such instances, renal biopsy should not be performed since the information gained is exceedingly un- likely to influence management, and the risks of the procedure are therefore not warranted. There are, however, circumstances in which renal biopsy is essential to establish a correct diagnosis, with im- portant implications for both management and prognosis. Biopsy should be considered when: • the history, examination, or laboratory tests suggest a systemic dis- order that could cause AKI and could be diagnosed by renal biopsy • urinalysis shows significant haematuria and proteinuria and/or the urine sediment contains red cell casts • the case history is atypical • renal failure is unusually prolonged (say beyond 6 weeks), al- though in this context cortical necrosis (see 'Renal cortical ne- crosis') is better diagnosed by CT scanning or angiography Nutrition Patients with AKI are invariably catabolic and derive a larger fraction of their energy expenditure from protein breakdown than normal. Insulin resistance, metabolic acidosis, the release of proteinases into the circulation, and changes in the metabolism of branched-chain amino acids have all been suggested as possible reasons. If nutri- tion is neglected, patients with AKI lose weight very rapidly, and those that lose most have the highest mortality, but it has not been proven in controlled trials that any form of nutritional support can alter mortality. Nevertheless, there is a consensus that early insti- tution of nutritional support probably improves prognosis. Despite this, and almost certainly to the patient's detriment, action is fre- quently delayed or not taken at all, particularly if it is thought that

21.5 Acute kidney injury 4819 the extra fluid load required will mandate the institution of dialysis or the need for additional dialysis sessions in an already busy unit. There is very little good evidence on which to base recommenda- tions. Enteral nutrition should be preferred to parenteral nutrition whenever possible, with KDIGO recommended daily adult re- quirements for those with AKI being total energy 20 to 30 kcal/kg body weight, with protein intake of 0.8 to 1.0 g/kg body weight (non catabolic patients not on dialysis), 1.0 to 1.5 g/kg body weight (patients on dialysis), up to a maximum of 1.7 g/kg body weight (catabolic patients, and those on continuous renal replacement therapy). If patients with AKI are oliguric, the nutritional support should be given in a restricted fluid volume, with reduced amounts of sodium, potassium, and phosphate. For practical purposes, it is sensible to have enteral and parenteral fluids that satisfy these needs available routinely (a variety of commercial preparations are avail- able): extra water and electrolytes can always be added when re- quired. In the many patients who are too unwell to take adequate food by mouth, commonly those who need it most, tube feeding or parenteral nutrition should be started early. Protein restriction, aimed at moderating the rise of serum urea, is not appropriate man- agement for patients with AKI. Bleeding In uraemia the bleeding time is prolonged, and in AKI this summates with any abnormality of haemostasis that might be simultaneously induced by the precipitating condition. Better control of uraemia and the routine use of H2-receptor antagonists have been associated with a greatly reduced risk of upper gastrointestinal bleeding, a pre- viously frequent and grave occurrence. Impairment of haemostasis is not a cause of great clinical concern in most patients, but there are some who bleed—from anywhere and everywhere. Guidelines for the management of such cases are given in Box 21.5.2. Sepsis Sepsis is a common cause of AKI, and outcome can be improved with prompt instigation of basic therapies, as described in the 'sepsis six' care bundle that emphasizes the following: • Administering high-flow oxygen to maintain target oxygen saturations at higher than 94% (unless the patient is at risk of hypercapnia) • Taking blood cultures • Giving intravenous antibiotics • Starting intravenous fluid resuscitation • Checking serum lactate • Monitoring hourly urine output In many more cases, however, the role of sepsis in the patient with AKI is insidious and difficult to diagnose with certainty. There is often a strong clinical feeling, but little in the way of hard proof, that sepsis underlies the slide towards worsening renal and multiorgan failure in patients who have been apparently successfully resusci- tated from major trauma or surgery, and septicaemia is the most common cause of death in those with AKI. The index of clinical suspicion must therefore be very high: if a patient with AKI ap- pears to be deteriorating in any way, the question must be asked: 'Is this sepsis?' Unused intravenous lines and urinary catheters should be removed, and those that are necessary but in any way suspicious should be replaced. The patient should be examined regularly for signs of a septic focus. There should be a low threshold for re- peated, thorough microbiological investigation. Proven infection should be treated promptly with appropriate antimicrobial agents (with the dose being modified as required). In many cases, how- ever, it will be necessary to start treatment 'blind', having taken specimens for culture and having made an educated guess as to the likely pathogen, with the possibility of Gram-negative septicaemia high on the list. In patients who appear 'obviously septic' or to be 'going off', but in whom no cause can be found, attention should be directed to- wards the abdomen, this being the most likely place for hidden mischief, either infective or ischaemic. Radiological investiga- tions, in particular CT scanning, can be very useful in searching for abdominal sepsis or dead bowel, but are not infallible: surgical exploration may be required, both to diagnose and to treat, espe- cially in patients whose renal failure follows previous abdominal surgical procedures. Prescription of drugs Many drugs are excreted by glomerular filtration or tubular secre- tion and must be given in reduced dosage or at longer intervals than normal in patients with renal failure (see Chapter 21.19). For patients with AKI, the following should not be given without very good reason: nonsteroidal anti-inflammatory drugs, ACE inhibi- tors, ARBs (all of which have adverse effects on renal perfusion and glomerular filtration), and aminoglycoside antibiotics (these are dis- cussed later in this chapter). A note about two other drugs that may be given to patients with AKI is also appropriate here: both aciclovir and penicillins can cause encephalopathy if given in the doses used to treat severe infection in patients with normal renal function. The dose of aciclovir needs to be reduced from between 5 and 10 mg/kg every 8 h to between 2.5 and 5 mg/kg every 24 h in those receiving renal replacement therapy, and physicians should restrain themselves from prescribing the maximum recommended doses of penicillins. If in doubt, consult the manufacturer's data sheet before prescribing any drug to a pa- tient with AKI. Specific causes of acute kidney injury A list of specific causes of AKI is given in Box 21.5.1: many of these are discussed in other chapters; those that are not are considered here. Box 21.5.2 Practical strategies for the management of bleeding in acute kidney injury 1 Exclude the possibility of a heparin effect 2 Blood transfusion to obtain haematocrit greater than 30% (very occa- sionally erythropoietin is of value) 3 Cryoprecipitate (10 bags) has its maximal effect between 1 and 2 h after administration. Its effect disappears at 24 to 36 h 4 Deamino-d-arginine vasopressin (DDAVP) (0.3 μg/kg intravenously) acts by increasing factor VIII coagulant activity. It has been shown in AKI to shorten prolonged bleeding time. Repeated doses have a lesser effect 5 Conjugated oestrogen: 0.6 mg/kg per day for 5 days. Shown to reduce bleeding time (for at least 14 days) in patients with chronic renal im- pairment and haemorrhagic tendency

section 21 Disorders of the kidney and urinary tract 4820 Prerenal failure and acute tubular necrosis Between 80 and 90% of the cases of AKI seen by physicians will fall into the categories of prerenal failure and acute tubular necrosis. The term 'prerenal failure' is used when renal dysfunction is entirely at- tributable to hypoperfusion, and where restoration of renal perfusion leads to rapid recovery. The term 'acute tubular necrosis' describes a clinical entity comprising AKI with three main characteristics: 1. It is seen in specific clinical contexts, frequently involving cir- culatory compromise and/or nephrotoxins. 2. Urinary abnormalities usually suggest tubular dysfunction. 3. Essentially complete recovery of renal function is expected within days or weeks in most cases if the patient survives the precipitating insult, with a period of polyuria commonly fol- lowing oliguria. The syndrome can be seen after virtually any episode of severe cir- culatory compromise, but not all causes of circulatory derangement are equally devastating to renal function. Primary impairment of cardiac performance, for example, following myocardial infarction, may cause serum creatinine to rise, but rarely causes renal failure of sufficient severity to require renal replacement therapy. By con- trast, an apparently similar haemodynamic upset caused by sepsis frequently does. Multiple insults are the rule rather than the excep- tion.

Circumstances associated with a particularly high risk of AKI include repair of a ruptured aortic aneurysm (20%, as opposed to 3% for elective repair), hepatobiliary surgery (10%), cardiac surgery (up to 20%, depending on case mix), pancreatitis (10%), and burns (2–38%, depending on the series). Pathophysiology The perfusion of the kidney seems to suffer more than that of any other organ when the circulation is compromised. In the face of modest underperfusion, the GFR is relatively preserved by a com- pensatory increase in the filtration fraction. This increase has re- percussions on tubular function which, along with other factors, leads to the increased tubular reabsorption of sodium, water, and urea—a situation rapidly reversed by restoration of renal perfusion. However, following prolonged circulatory shock, renal function fre- quently deteriorates in a manner that is not immediately reversible, and it is not at all obvious why this should be so. Lack of a clear pathophysiological understanding has bedevilled attempts at the de- velopment of rational therapy. Under normal conditions the kidney enjoys high blood flow, exceeded on a volume/weight basis only by the carotid body, and oxygen tension in the renal venous effluent is high, suggesting that oxygen supply greatly exceeds demand. Such a situation might be expected to confer protection from the effects of circulatory com- promise, but no such benefit is observed: indeed the kidney appears to be more susceptible to damage than other organs, with the typ- ical histological features of acute tubular necrosis being effacement and loss of the brush border of the proximal tubule (particularly in the S3 segment), patchy loss of tubular cells, and casts in the distal tubule. AKI similar to this can be produced in animal models by ischaemia, and the condition often arises clinically in the setting of profound haemodynamic disturbance, leading to the supposition that—despite apparently generous blood flow normally—renal is- chaemia is the cause of renal failure in such circumstances. At the ‘whole-organ’ level, two main hypotheses, not mutually ex- clusive, have been proposed to explain the kidney’s vulnerability to ischaemic damage. First, the specialized anatomical arrangement of the vasa rectae that is essential for the countercurrent mechanism involved in urinary concentration and dilution leads to arterio- venous shunting of oxygen and the presence of areas of profound hypoxia (Po_2 10–20 mmHg) within the normal kidney. These areas are operating on the verge of anoxia in the normal organ and hence might be susceptible to ischaemic damage in response to a modest compromise of whole-organ blood flow. Second, there is clinical and experimental evidence of intense constriction of renal vessels during shock, hence very severe reduction in renal blood flow (perhaps only transient) may be responsible for the initiation of ischaemic damage. The justification for many of the interventions proposed in the man- agement of patients at risk of AKI, or with established AKI, is that they might preserve renal blood flow and/or reduce renal oxygen consumption, thus rendering the development of ischaemic injury less likely. At a cellular level, a wide variety of pathophysiological mech- anisms are involved. Endothelial cell injury arising directly from ischaemia or various inflammatory processes causes disruption of microvascular blood flow. Poor tissue oxygenation leads to epithelial cell injury via mechanisms including intracellular ac- cumulation of calcium, generation of reactive oxygen species, ac- tivation of various proteases and phospholipases, and depletion of ATP. These lead to a range of consequences such as redistribution of tubular membrane proteins, sloughing of viable cells into the tubular lumen, and apoptosis. Recent work has drawn attention to the involvement of immunological factors (complement activa- tion, intercellular adhesion molecules, inflammatory mediators) and receptors on tubular cells (peroxisome proliferator-activated receptor β, toll-like receptors, bradykinin receptors), some of which may in the future provide opportunity for therapeutic intervention. Once damage to the kidney has been sustained, a variety of fac- tors may be responsible for the persistence of excretory failure that is characteristic of the clinical syndrome of acute tubular necrosis. These include activation of tubuloglomerular feedback (increased delivery of sodium chloride to the macula densa leads to reduction in GFR), back-leak of filtrate from damaged tubules, and tubular obstruction by casts. Even in experimental models it is very hard to determine what is happening at any time, and impossible to do so in clinical practice. However, many of the ab- normalities have a structural as well as a functional basis, hence rapid reversal cannot be expected, there being good evidence that recovery from acute tubular necrosis depends on cellular regeneration. Diagnosis The diagnosis of prerenal failure/acute tubular necrosis is based on the clinical context, which often involves circulatory compromise, and the exclusion of obstruction or renal inflammatory conditions, usually by ultrasound examination of the urinary tract and testing of the urine for blood and protein, respectively. Prerenal failure and acute tubular necrosis can best be regarded as a continuum of renal response to ischaemic injury, in much the same way that stable angina, non-ST-elevation myocardial infarc- tion, and ST-elevation myocardial infarction are a continuum of

21.5 Acute kidney injury 4821 cardiac response to ischaemia. A simple analysis emphasizes that at the prerenal end of the spectrum the biochemical composition of the urine reflects the response of normal tubules to impaired renal perfusion. There is avid retention of sodium and water, leading to low urinary sodium and high urinary urea and creatinine concen- trations, together with a high urinary osmolarity. By contrast, at the acute tubular necrosis end of the spectrum the tubules are damaged and unable to sustain large sodium or osmolar gradients, hence urinary sodium concentration is elevated and the urinary urea and creatinine concentrations and urinary osmolarity are relatively low. However, this simple analysis is flawed and biochemical ana- lysis of the urine is rarely useful in clinical practice, as explained in Table 21.5.7. From a practical point of view, treatment is begun on exactly the same lines whether the expected diagnosis is of prerenal failure or of acute tubular necrosis. The response to resuscitation retrospectively defines the diagnosis—restoration of renal per- fusion leads to rapid improvement in renal function in prerenal failure—and determines further management. Over the past 20 years (and more), the measurement of urinary or plasma/serum levels of a variety of proteins (e.g. urinary kidney injury molecule-1, plasma and urinary neutrophil gelatinase- associated lipocalin (NGAL), and many others) have been explored as possible early markers of acute tubular necrosis. None has yet been found useful in clinical practice. Two uncommon circumstances in which measurement of urinary sodium concentration may be helpful are (1) hepatorenal syndrome, when urinary sodium concentration is typically low (<10 mmol/ litre), although this is not a major diagnostic criterion of the condi- tion; and (2) acute renal artery occlusion (bilateral or of single func- tioning kidney) when urinary sodium concentration can equal that in serum. Circumstances predisposing to prerenal failure are almost invari- ably associated with raised serum levels of antidiuretic hormone. This acts on the collecting duct to increase the tubular reabsorption of both water and urea, hence the serum concentration of urea rises out of proportion to that of creatinine in prerenal failure. Serum urea may also appear to be disproportionately raised in the presence of sepsis, steroids, tetracycline (catabolic effect), and gastrointes- tinal haemorrhage (protein meal, perhaps inducing catabolism due to absence of the essential branched chain amino acid isoleucine in haemoglobin). Prevention Key elements have been described previously in this chapter in ‘Prevention of acute kidney injury’. Clinical findings There are no specific clinical features of prerenal failure or acute tubular necrosis. There may be symptoms of AKI, as described pre- viously, but these are also not specific and are rarely prominent, hence the clinical picture at presentation is likely to be dominated by signs of volume depletion and those of the precipitating condition. If the patient does not die of AKI, either because the degree of uraemia is modest or renal replacement therapy is provided, then renal recovery occurs in the vast majority of those who survive the precipitating insult. This may begin at any time from a few days to a few months (median 10–14 days) after the onset of the condition, with a progressive increase in urinary volume typically preceding improvement in the serum levels of creatinine and urea. Due to a relatively persistent defect in renal tubular sodium reabsorption and concentrating ability, a period of polyuria may ensue, placing the patient at risk of sodium and water depletion. Specific treatment The importance of effective treatment of the underlying condition and of rapid correction of hypovolaemia are above clinical dispute, although neither has been subject to controlled trial as regards the outcome of prerenal failure or acute tubular necrosis. There is no strong evidence that any other pharmacological agent is beneficial, and following the publication of a number of randomized controlled trials, the use of agents such as loop diuretics (e.g. furosemide), dopamine (or fenoldopam, a selective dopamine D1 partial agonist), and mannitol cannot be recommended. In experimental models of acute tubular necrosis, the use of growth factors has been shown to speed up renal recovery: this offers some hope for the future, but no benefit has yet been shown in anything other than pilot clinical studies, and such agents (including erythropoietin) should not be given for this indication outside properly conducted clinical trials. Prognosis The prognosis of patients with AKI, most of whom will have prerenal failure or acute tubular necrosis, has been described previously in this chapter in ‘Epidemiology’. Series from intensive care units of patients who require renal replacement therapy for acute tubular necrosis, commonly in the context of respiratory failure requiring mechanical ventilation, typically report mortality rates of 40 to 60%. Death should rarely be attributable to a primary sequel of renal failure (e.g. uraemia or hyperkalaemia) and the incidence of life- threatening gastrointestinal haemorrhage is much reduced: sepsis is the major killer. Most patients die with, but not directly of, renal failure. Assuming survival from the precipitating insult, complete re- covery of renal function can be anticipated in almost all patients aged less than 65 years with pre-existing normal renal function and acute tubular necrosis of short duration. This is not so for older pa- tients, those with pre-existing chronic kidney disease, or those who have prolonged acute tubular necrosis (>4-week requirement for renal replacement therapy). In the largest reported series of patients with AKI, 11 to 12% of survivors of ‘medical’ or ‘surgical’ AKI (pre- sumed to have acute tubular necrosis) required long-term dialysis. Table 21.5.7 ‘Typical’ urinary biochemical indices in prerenal failure and acute tubular necrosis, and why they are rarely useful Index ‘Typical’ prerenal failure ‘Typical’ acute tubular necrosis Urinary sodium (mmol/litre) <20

> 40 Urine osmolarity (mOsm/litre) 500 <350 Urine:serum urea 8 <3 Urine:serum creatinine 40 <20 Fractional sodium excretion <1% 2% There are several reasons why urinary biochemical indices are of very limited clinical use: (1) intermediate values are common; (2) ‘typical’ values do not reliably predict renal prognosis—it is recognized that cases that are otherwise indistinguishable from ‘typical’ acute tubular necrosis can have a low urinary sodium concentration; (3) diuretics and pre-existing tubular disease will impair the ability of tubules to retain sodium in prerenal failure; and (4) treatment is not dictated by urinary indices.

section 21 Disorders of the kidney and urinary tract 4822 Nephrotoxins Exogenous nephrotoxins A wide variety of exogenous agents, including therapeutically pre- scribed drugs, can cause AKI (Box 21.5.3). Poisoning by drugs and chemicals are discussed in Chapter 10.4.1; envenoming and poi- soning by animals or plants are discussed in Chapters 10.4.2 and 10.4.3. Other causes listed in Box 21.5.3 that are worthy of par- ticular note are discussed here. Aminoglycosides The nephrotoxicity of particular aminoglycosides is related to the strength of their positive charge. They are freely filtered by the glom- eruli, with 90 to 95% passing into the urine, but 5 to 10% is retained in the renal cortex as a result of binding to negatively charged mem- brane phospholipids in parts S1 and S2 of the proximal tubule (and S3 in the presence of renal ischaemia). Here they are delivered to megalin (the Heymann nephritis autoantigen, a member of the low- density lipoprotein receptor family) in coated pits, endocytosed and trafficked to the endosome of proximal tubular cells, where at a con- centration vastly exceeding the serum level they inhibit fusion in vivo and in vitro. Gentamicin is nephrotoxic, as are tobramycin, amikacin, netilmicin and streptomycin to progressively lesser degrees. The risk of nephrotoxicity is increased by old age, chronic kidney disease, high dosage, prolonged treatment, combined treatment with other nephrotoxic drugs, renal ischaemia, and volume depletion. A 50% rise in serum creatinine from baseline is seen in 10 to 20% of patients, even when monitoring optimally controlled drug levels. Parenteral administration is not required for the development of toxicity: AKI can occur as a result of systemic absorption when aminoglycosides are used in irrigating or bowel-sterilizing solutions. The typical clinical picture is of relatively mild nonoliguric renal failure coming on about 1 week after starting treatment. The urine typically shows low-level proteinuria, with hyaline or granular casts. Hypokalaemia, hypomagnesaemia, hypocalcaemia, and hypophosphataemia are sometimes seen, and also a Fanconi’s syndrome. Recovery typically occurs over about 3 weeks after the aminoglycoside is stopped, but this may be delayed or incomplete. Differentiating aminoglycoside-induced AKI from other causes of acute tubular necrosis can be difficult or impossible. Patients are given aminoglycosides because of sepsis, and many will have other significant comorbidities, other acute medical problems, and have been exposed to other potential nephrotoxins (e.g. radiocontrast agents). Aminoglycosides should only be used in the relatively uncommon circumstance that there is no suitable alternative antibiotic that is not nephrotoxic. The risk of nephrotoxicity can be reduced by choosing the least toxic aminoglycoside possible, ensuring that the patient is not volume depleted, correcting hypokalaemia and hypomagnes- aemia, using a once-daily dosing regimen, adjusting the dose ac- cording to renal function, monitoring serum drug levels, limiting the duration of therapy to 7 to 10 days, and minimizing the use of other nephrotoxic drugs. Anionic polyaminoacids (e.g. polyaspartic acid) can interfere with the binding of cationic aminoglycosides to proximal tubular cell membranes and lysosomes and may be useful in preventing aminoglycoside nephrotoxicity, but this approach is not used clinically. Radiographic contrast media Studies in animal models suggest that radiographic contrast media can cause acute tubular necrosis. The mechanism is uncer- tain: favoured hypotheses include by induction of intramedullary vasoconstriction or by direct cytotoxic effect. The incidence of AKI associated with the use of radiographic con- trast media has been reported to vary between 0 and 50%, reflecting many variables. Patient risk factors include pre-existing chronic Box 21.5.3 Some nephrotoxins that can cause acute kidney injury (excluding causes of interstitial nephritis) Exogenous • Antibiotics:

— Aminoglycosides

— Tetracyclines

— Cephaloridine

— Amphotericin B

— Sulphonamides

— Polymyxin/colistin

— Bacitracin

— Pentamidine

— Vancomycin • Radiocontrast media • Anaesthetic agents:

— Methoxyfluranea

— Enfluranea • Chemotherapeutic/immunosuppressive agents:

— Ciclosporin

— Cis-platinum

— Methotrexate • Organic solvents:

— Glycols (e.g. ethylene glycola)

— Hydrocarbons (e.g. carbon tetrachloride, toluene) • Poisons:

— Venoms (snake bite, e.g. Russell's viper)

— Stings

— Insecticides/herbicides/rodenticides (including paraquat, copper sulphate, and sodium chlorate)

— Mushrooms (amanita)

— Hemlock

— Carp bile

— Herbal medicines • Drugs of abuse • Heavy metals Endogenous • Pigments:

— Myoglobin

— Haemoglobin • Intrarenal crystal deposition:

— Urate

— Phosphate (tumour lysis syndrome) • Tumour related:

— Immunoglobulin light chains In many instances, nephrotoxicity arises both from a direct toxic action on renal tissue and from indirect systemic effects. a May be associated with intratubular precipitation of oxalate crystals.

21.5 Acute kidney injury 4823 kidney disease, diabetic nephropathy, cardiac failure, hypovolaemia, and myeloma. Procedural risk factors include dose and type of con- trast agent, and the type of procedure (interventional procedures are higher risk than diagnostic). As with aminoglycosides, differentiating contrast-induced AKI from other causes of acute tubular necrosis can be difficult or im- possible, and contrast exposure may be one of many contributing factors to AKI in some patients. In patients who develop AKI after angiography, particular consideration should be given to the dis- tinction between contrast nephropathy and atheroembolic renal disease. Features suggesting the latter include embolic lesions (e.g. ‘trash foot’), eosinophilia, hypocomplementaemia, delayed onset of AKI, and little or no recovery of AKI (see Chapter 16.14.3). When renal impairment does develop, it typically occurs 12 to 24 h after exposure, is nonoliguric and usually mild, and recovery begins within 3 to 5 days. Recent prospective studies, using nonionic contrast media and in which careful attention has been paid to the maintenance of adequate hydration, have shown a very low incidence of significant renal im- pairment, even in groups reported to be at high risk (diabetes, mye- loma). Concern about nephrotoxicity of radiocontrast media should very rarely, if ever, restrict the selection of imaging technique in a particular patient: if there is diagnostic uncertainty, then they re- quire the imaging technique most likely to achieve a diagnosis; if there is no diagnostic uncertainty, then no imaging is needed. With regard to prevention, there is no very strong evidence on which to base recommendations. Standard practice is to advise that patients with an estimated GFR less than 60 ml/min and additional risk factors (e.g. significant proteinuria, diabetes, heart failure, liver failure, and myeloma) and all patients with an estimated GFR less than 45 ml/min who are to be given intra-arterial contrast agents (for nonemergency purposes) should avoid volume depletion, avoid nonsteroidal anti-inflammatory drugs (NSAIDs), be given a periprocedural infusion of isotonic saline, and be given the lowest effective dose of an iso-osmolal contrast agent. There is no good evidence to support the use of N-acetylcysteine or any other agent in attempting to prevent contrast-induced nephropathy, and a meta-analysis of 11 studies showed no benefit of haemodialysis or haemofiltration/haemodiafiltration in preventing the condition.
Endogenous nephrotoxins Myoglobin Myoglobinuric AKI, the mechanism of which is incompletely understood (but probably involves a combination of volume de- pletion/renal ischaemia, tubular injury by free iron/haem, and tubular obstruction by haem pigment casts), is typically associated with crush injury to muscle, most typically after patients have been trapped under rubble following earthquakes or explosions, but there are a large number of causes of nontraumatic rhabdomyolysis (Box 21.5.4). As might be expected, genetic causes are most likely with young age of presentation: whole-exome sequencing found mutations that were thought to be pathogenic in 8 of 58 candi- date genes in 9 of 21 (43%) children and adolescents with rhabdo- myolysis in a study in Israel. A high index of suspicion is required to diagnose cases that are not obviously associated with muscle injury, since muscular pain, swelling, and tenderness may not be prominent features and can even be absent. The key to making the diagnosis is to detect myo- globin in the urine, or a very high level of enzymes released from muscle in the plasma. The former is recognized by the combination of dark-brown (‘Coca-Cola’) urine that tests positive for ‘blood’ on a reagent strip, but

which does not contain red cells on microscopy, although pigmented 'muddy' granular casts are seen. The muscle enzyme usually measured in serum is creatine kinase: the normal range of this is up to just below 200 U/litre; in rhabdomyolysis values above 10 000 U/litre are typical, a value of only 1000 to 2000 U/litre not being enough to establish the diagnosis of rhabdomyolytic AKI in the absence of other supporting evidence. Extremely high levels of serum myoglobin, aldolase, and lactic dehydrogenase are also seen, all being released from damaged muscle. Rhabdomyolysis can be associated with very high serum levels of potassium, phosphate (>2.5 mmol/litre), urate (>750 μmol/litre), as- partate transaminase (in the many hundreds of U/litre, exceptionally in the thousands), and alanine transaminase (in the few hundreds of U/litre), and with an unusually low serum calcium concentration Box 21.5.4 Some causes of rhabdomyolysis • Direct muscle injury • Ischaemic muscle injury:

— Compression

— Vascular occlusion • Any cause of coma (e.g. opioid overdose, diabetes mellitus, or cere- brovascular accident) or of prolonged restraint/immobility (e.g. fol- lowing a fall in older people) can be associated with rhabdomyolysis due to a pressure effect • Excessive muscular activity:

— Seizures

— Sport (e.g. marathon running) • Inflammatory myositis:

— Immunological (e.g. dermatomyositis and polymyositis)

— Infection (e.g. viral: influenza, coxsackie, and HIV) • Metabolic:

— Hypokalaemia, hypophosphataemia • Genetic:

— Disorders of fatty acid metabolism (e.g. CPT2)

— Disorders of glycogen metabolism and storage (e.g. PFKM, PGAM2, and PYGM—McCardle's syndrome)

— Disorders of skeletal muscle relaxation and contraction (e.g. CACNA1S, MYH3, RYR1, and SCN4A)

— Disorders of purine metabolism (e.g. AHCY) • Endocrine:

— Diabetic ketoacidosis/nonketotic hyperglycaemia

— Hypothyroidism • Toxins/drugs:

— Snake bite, carbon monoxide, alcohol, hemlock, and paint/glue sniffing

— Clofibrate, aminocaproic acid, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) • Others:

— Sickle cell trait

— Near drowning

— Hypothermia

— Malignant hyperpyrexia

— Neuroleptic malignant syndrome

— Phaeochromocytoma ‘storm’

section 21 Disorders of the kidney and urinary tract 4824 (<1.5 mmol/litre). Any of these findings should lead to serious con- sideration of rhabdomyolysis in any patient with unexplained AKI. Aside from treatment (when possible) of the underlying cause, including decompression of compromised muscle compartments and stopping any drugs that might be contributing to the problem, initial management involves correction of intravascular volume depletion, which may be massive due to sequestration of fluid in damaged muscle, and provocation of a diuresis of around 200 ml/h while myoglobinuria persists, the intention being both to establish good renal perfusion and ‘wash out’ obstructing casts. This can be achieved by infusion of 0.9% saline or other balanced salt solution (e.g. Hartmann’s), initially at a rate of 1 to 2 litre/h, titrated down at the first sign of fluid overload (pulmonary oedema) or—if and when the patient becomes massively polyuric—to maintain a urinary output of 200 to 300 ml/h. When this urinary output is achieved, many physicians would recommend additional infusion of bicar- bonate and mannitol to sustain a forced alkaline-mannitol diuresis, with urinary pH above 6.5, the argument being that this might reduce the renal toxicity of myoglobin. The evidence that this is beneficial is not very substantial, and care must be taken to monitor for (with bicarbonate) hypokalaemia and hypocalcaemia, and (with man- nitol) hypernatraemia and hyperosmolality. The serum potassium concentration can rise by more than 1 mmol/litre per day, hence hyperkalaemia is the usual indication for renal replacement therapy. Assuming that the patient survives the precipitating insult, hypercalcaemia develops in 20 to 30% of cases during the recovery phase. This is thought to be caused by mobilization of calcium from injured muscle, correction of hyperphosphataemia with improve- ment in GFR, and an increase in 1,25-dihydroxyvitamin D (mech- anism uncertain). Haemoglobin AKI can be seen in association with massive haemolysis in many circumstances, but these are relatively rare in the developed world, where ABO-mismatched blood transfusion is probably the most common cause. By contrast, a study in Chandigarh (north India) re- ported in 1977 that haemolysis was found in over 20% of 325 patients receiving dialysis for AKI, but recent reports suggest a lower preva- lence. Haemolysis is most frequently seen in those with glucose-6- phosphate dehydrogenase deficiency, with snake bite and malaria the next most common causes. Copper sulphate poisoning, wasp stings, arsine poisoning, burns, and as a complication of bladder ir- rigation with hypotonic solutions are other causes. In each circumstance it is thought that the development of AKI is exacerbated by (if not solely caused by) the presence of large amounts of free haemoglobin within the circulation. As with rhabdomyolysis, the urine is coloured red to brown, with pigmented granular casts on microscopy, but the findings in the plasma/serum are different: it is reddish in colour (whereas it is usually clear in rhabdomyolysis), creatine kinase is not elevated, haptoglobin levels are reduced, and the peripheral blood film is abnormal. The approach to renal man- agement is as described previously for rhabdomyolysis. Urate and other endogenous nephrotoxins The tumour lysis syndrome is associated with a rapid rise in plasma uric acid concentration (and almost certainly liberation of other nephrotoxins) as a complication of the treatment of lymphoma, leukaemia, myeloma, or other ‘high-turnover’ tumours. Hyperuricaemia and renal failure have been described on rare occasions after recurrent epileptic seizures. Prevention and management of tumour lysis syndrome are discussed in Chapter 21.10.5, as is AKI associated with myeloma. Vascular causes Renal cortical necrosis Renal cortical necrosis is an uncommon cause of AKI, accounting for around 1% of cases in the developed world, but more in the developing world, although its incidence here appears to be decreasing. A large centre in north India reported it to be the cause of 3.8% of cases of incident AKI. A study of 2405 cases of community- acquired AKI in eastern India reported an incidence of 5.8% in 1983 to 1995, falling to 1.3% in 1996 to 2008. However, these figures may be an underestimate, given that investigation is not pursued in many patients who fail to recover from what was presumed to be acute tubular necrosis on the grounds that test results do not reliably pre- dict prognosis or affect management, which is supportive. Renal cortical necrosis presents in the same context as acute tubular necrosis, which is almost always the diagnosis made initially on clinical grounds. Suspicion should arise immediately if a patient without obstruction is anuric, as was found in 79% of 113 patients in the largest study reported, but cortical necrosis is often considered only when renal function fails to improve. Most cases of renal cortical necrosis are the result of obstetric disasters, particularly postpartum haemorrhage, placental abrup- tion, eclampsia, septic abortion, or puerperal sepsis. Snake bite, haemolytic uraemic syndrome, acute gastroenteritis, pancreatitis, septicaemia (often with disseminated intravascular coagulation), trauma, and drug-induced intravascular haemolysis are risk factors in the nonobstetric population. The pathological findings are of microvascular thrombosis, mainly affecting interlobular arteries, arterioles, and glomeruli, with complete infarction of affected areas of cortex. The medulla and a rim of juxtamedullary tissue are spared. Investigations to establish the diagnosis of renal cortical ne- crosis are renal angiography, contrast-enhanced CT scanning or dimercaptosuccinic acid (DMSA) scan. Angiography reveals attenu- ation of interlobular arteries, an increase in the subcapsular vessels, and a negative outer cortical nephrogram. CT scanning shows en- hancement of the renal medulla, but no enhancement of the renal cortex and no excretion of contrast. DMSA scanning typically demonstrates small sections of viable cortex surrounded by a wide- rimmed photopenic area of cortical loss. Renal biopsy necessarily samples only a very small piece of tissue and may mislead because of the patchy nature of renal damage. In the months or years after an episode of renal cortical necrosis, the kidneys tend to contract: cortical calcification producing an eggshell or tramline appearance on the abdominal radiograph is a characteristic sequel, but this is not useful in making the diagnosis acutely. Return of renal function in cases of renal cortical necrosis oc- curs very slowly, if at all, and is attributable to the survival of islands of intact cortical tissue. About 50% of patients recover sufficiently to come off dialysis, but the GFR rarely exceeds 10 to 20 ml/min. Hypertension (including accelerated phase) may be a significant problem, and a subsequent decline in renal function with the neces- sity for a return to dialysis/transplantation is not uncommon.

 Large-vessel occlusion Arterial occlusion Occlusion of the main renal arteries—or of the artery supplying a solitary functioning kidney—by embolism (usually in the context of atrial fibrillation), trauma, dissection, or thrombosis may rarely be the reason for AKI. A meta-analysis of outcomes following endovascular abdominal aortic aneurysm repair found renal in- farcts in 6.6% of cases with suprarenal fixation and 2.3% of cases with infrarenal fixation. Loin or abdominal pain usually occurs, sometimes there is nausea and vomiting, and occasionally fever, but symptoms can be notable by their absence. Suspicion should be aroused by complete, sudden anuria in the absence of urinary obstruction, especially if the clinical setting is appropriate (e.g. atrial fibrillation in an arteriopath). There may be acute elevation of blood pressure. Urinalysis may reveal proteinuria and haematuria. A useful pointer to the diagnosis is the finding of a urinary sodium concentra- tion similar to that of serum. Serum lactate dehydrogenase is often more than two to four times the upper limit of normal, which sug- gests renal infarction when seen in an appropriate clinical context in conjunction with normal or near-normal serum aminotransferases. The test that confirms the diagnosis is usually contrast-enhanced CT scanning, revealing an absence of renal perfusion or a wedge-shaped defect. Renal angiography and DMSA scanning can also establish the diagnosis, but the latter is rarely undertaken in the acute setting. There is no good evidence on which to base management recom- mendations. Anticoagulation with therapeutic dose low molecular weight heparin followed by warfarin or a nonvitamin K antagonist oral anticoagulant is indicated if there is recognized clinical indica- tion (e.g. atrial fibrillation). If the diagnosis of renal arterial occlu- sion due to thromboembolism or renal artery thrombosis is made within 1 to 2 days of symptom onset, most nephrologists would ad- vise percutaneous endovascular therapy with local thrombolysis, thrombectomy, or stent placement. Surgery is very rarely indicated in the acute setting, but there are reports of surgical bypass restoring renal function and controlling hypertension when undertaken many weeks after arterial occlusion in those with atherosclerotic renovascular disease in whom (prior to occlusion) a collateral blood supply to the renal parenchyma had developed. This should only be considered when the function of the arterially occluded kidney is critical (e.g. there is no contralateral functioning kidney), the affected kidney has preserved volume (not small and shrunken), and imaging suggests that the renal paren- chyma is not infarcted, albeit that perfusion is inadequate to sustain glomerular filtration. Venous occlusion Renal vein thrombosis can cause AKI, most commonly in adults as a complication of nephrotic syndrome, but in infants and children as a result of abdominal sepsis or severe dehydration. Acute renal vein thrombosis typically presents with loin pain, nonvisible or visible haematuria, and (when bilateral or affecting a single functioning kidney) with AKI. Chronic renal vein thrombosis may present with rising serum creatinine but is usually asymptom- atic. As with arterial occlusion, renal venous occlusion often leads to a rise in serum lactate dehydrogenase without concomitant ele- vation of aminotransferases. Definitive diagnosis requires renal imaging, usually with ultrasonography, CT, or magnetic resonance imaging depending on local practice. Selective renal venography is rarely required. Patients with acute renal vein thrombosis associated with AKI should be considered for local thrombolytic therapy with/without catheter thrombectomy. Other patients with renal vein thrombosis should be offered anticoagulation, as for pulmonary embolism, un- less contraindicated. Small-vessel occlusion Accelerated-phase hypertension ‘Accelerated-phase’ hypertension (a term preferred to ‘malignant’ hypertension because the implication of malignancy is terrifying for patients) occurs when the blood pressure is elevated sufficiently to cause fibrinoid necrosis of blood vessels, leading to the development of haemorrhages and exudates in the ocular fundi. It may develop as a consequence of pre-existing renal disease and is itself a potent cause of renal damage. AKI is a common complication in those with previously normal renal function, and is associated with proteinuria, haematuria, and the presence of urinary red cell casts. The higher the creatinine at presentation, the poorer the prognosis for both patient survival and renal outcome: in one study, only 9% of those with an initial serum creatinine below 300 μmol/litre progressed to need renal replacement therapy, compared with two-thirds of those with a serum creatinine above this level. The ability of the kidney to autoregulate perfusion is disturbed in accelerated-phase hyperten- sion, hence the therapeutic lowering of arterial pressure may be as- sociated with reduced renal perfusion and an abrupt decline in renal function. Accelerated-phase hypertension is one of the conditions in which renal function sometimes recovers after a lengthy period on dialysis. Renal failure was the cause of two-thirds of the deaths in pa- tients with accelerated-phase hypertension in the days before dialysis was available. See Chapter 16.17.5 for further discussion. Systemic sclerosis A syndrome resembling accelerated-phase hypertension and termed 'scleroderma renal crisis' affects 5 to 20% of patients with diffuse cutaneous systemic sclerosis, use of prednisolone of greater than 15 mg/day, and presence of RNA polymerase antibodies being additional risk factors. It usually occurs within the first 5 years of the disease, may be the presenting feature, and often appears during the winter months. Rapid worsening of skin manifestations may precede the crisis, but frequently there is no warning. The patient may de- velop headaches, visual disturbance, and convulsions. Arterial pres- sure is usually grossly elevated, but the renal syndrome can occur without extreme hypertension in those with low baseline blood pressure. Haemorrhages and exudates are often seen in the ocular fundi. Urinalysis can be unremarkable or show low-level proteinuria and/or nonvisible haematuria. Renal failure develops rapidly. Renal biopsy is not required for diagnosis, but the typical renal histology is of concentric 'onion skin' intimal proliferation and thickening that leads to narrowing and occlusion of small arcuate and interlobular arteries. A microangiopathic haemolytic anaemia may complicate the situation. First-line treatment is with ACE inhibition, which should be con- tinued even in the face of an initial rise in serum creatinine and per- sisted with in the long term. A study of 145 ACE inhibitor-treated patients reported that 62% required dialysis, but many of these were able to discontinue it, sometimes many months later. By contrast,

section 21 Disorders of the kidney and urinary tract 4826 discontinuation of dialysis was rarely reported in historical pre-ACE inhibitor series. See Chapter 19.11.3 for further discussion. Glomerulonephritic and vasculitic causes A large number of glomerulonephritic and vasculitic diseases can cause AKI, sometimes in association with pulmonary haemorrhage. These are discussed in detail in the relevant subchapters of Chapter 21.8, and in Chapters 20.10.2 and 20.10.3. Together they form only 5 to 10% of cases of AKI, but making the correct diagnosis is of extreme im- portance because of the management implications. Regrettably, most nephrologists have seen cases where the diagnosis has been much delayed because renal impairment has incorrectly been attributed to acute tubular necrosis, and infiltrates on the chest radiograph to oe- dema or infection. This error, which can be catastrophic, should be avoided in patients in whom the cause of AKI is not obvious by an approach to management as outlined in Box 21.5.5. The possible presence of a rapidly progressive glomerulonephritis/ vasculitis is a medical emergency. Antiglomerular basement mem- brane disease responds well to immunosuppression with plasma exchange, steroids, and cyclophosphamide, but only if treatment is begun before dialysis is required. Immunosuppressive treatment should be given as early as possible in the course of AKI complicating microscopic polyangiitis/idiopathic rapidly progressive (crescentic) glomerulonephritis, granulomatosis with polyangiitis (previously known as Wegener's disease), and systemic lupus erythematosus. The urgency is such that it may well be appropriate to start these treatments while the results of blood tests and renal biopsy are awaited, and to stop them if the findings do not corroborate the ini- tial clinical diagnosis. The management of these patients is complex and patients benefit from the judgement and expertise of specialists. Acute interstitial nephritis Acute interstitial nephritis is discussed in Chapter 21.9.1. Lepto spirosis (Chapter 21.11) and hantaviral infection (Chapter 21.10.8) are both associated with AKI and acute interstitial nephritis: the fol- lowing account is to aid the clinician in distinguishing between them. Leptospirosis The diagnosis of leptospirosis should be considered in any patient with unexplained

AKI who has myalgias/muscle tenderness, con- junctival injection, and/or haemorrhage and/or jaundice. Direct enquiry must be made as to whether any such patient has been exposed to rats. Blood tests commonly reveal a dramatic conju- gated hyperbilirubinaemia (often >250 μmol/litre) and thrombo- cytopenia (seen in 40% of cases), and there may also be elevation of serum creatine kinase and a slight increase in serum aspartate aminotransferase. Anaemia may be severe due to intravascular haemolysis. By contrast to most other causes of AKI, serum po- tassium is often normal or low in cases of leptospirosis. Mild ab- normalities of blood clotting tests can be seen, but disseminated intravascular coagulation is not a feature, which is an important point in distinction from bacterial septicaemia. Hantavirus disease In Europe In Europe, the Puumala serotype of hantavirus produces an illness that can have many similarities to that produced by leptospirosis, although serological studies indicate that many patients must have a subclinical infection. In those that are symptomatic, high fever is typically followed within a couple of days by loin/abdominal pain and often by nausea and vomiting; photophobia and signs of meningeal irritation can also occur. AKI follows when these symptoms have settled and is associated with conjunctival haem- orrhage (20%), proteinuria (almost 100% of cases), nonvisible haematuria (70%), thrombocytopenia (50%), and a transient mild rise in plasma liver enzymes. There may be a small increase in serum bilirubin (maximum 40 μmol/litre). Mild abnormalities of blood clotting tests are seen, but disseminated intravascular co- agulation is rare. Renal biopsy, performed for the indication of unexplained acute renal impairment, shows interstitial nephritis. This has no pathog- nomonic features, leading in this clinical context to the differential diagnosis of leptospirosis and sometimes (depending on exposure) disease induced by NSAIDs. Leptospirosis is much more likely if the serum bilirubin is markedly elevated. NSAID-induced disease does not cause conjunctival haemorrhages or thrombocytopenia. The diagnosis of Puumala hantavirus infection is made on the basis of serological evidence. Prognosis is good: no deaths have been re- ported and renal function returns to normal. Box 21.5.5 Diagnosis of glomerulonephritic and vasculitic causes of acute kidney injury 1 A history and examination specifically directed towards determining whether a glomerulonephritic or vasculitic illness might be present. 2 Stick testing of the urine for blood and protein, followed (if positive) by microscopy to look for the presence of cellular casts. 3 The following tests:

— Measurement of serum antiglomerular basement membrane anti- bodies—positive in Goodpasture’s disease (see Chapter 21.8.7).

— Measurement of serum antineutrophil cytoplasmic antibodies (ANCA) (screening by indirect immunofluorescence test, specific tests for antiproteinase-3 and antimyeloperoxidase antibodies)—usually positive in microscopic polyangiitis and granulomatosis with polyangiitis (see Chapter 21.10.2).

— Estimation of serum complement levels (C3 may be depressed in postinfectious glomerulonephritis, mesangiocapillary glomerulo- nephritis, and systemic lupus erythematosus) (see Chapters 21.8.5, 21.8.6, and 21.10.3).

— Measurement of serum antistreptolysin-O titre—elevated in poststreptococcal glomerulonephritis) (see Chapter 21.8.5).

— Serological tests for systemic lupus erythematosus (see Chapter 21.10.3).

— Estimation of serum immunoglobulins and testing for urinary light chains (see Chapter 21.10.5).

— Estimation of serum cryoglobulins (see Chapter 21.10.5). 4 Consideration of the possibility that pulmonary infiltrates in a patient with AKI might be due to haemorrhage; the chances of this are in- creased if there is a history of haemoptysis (associated with several forms of rapidly progressive glomerulonephritis), nasal discharge or bleeding (associated with granulomatosis with polyangiitis), or if an- aemia is unusually profound and otherwise unexplained; lung func- tion tests demonstrating an increase in carbon monoxide transfer factor can establish the diagnosis but may be impractical in a patient who is very ill. 5 An urgent renal biopsy in any patient with AKI and an active urinary sediment unless the diagnosis is clear or there is a strong contraindica- tion (e.g. a single kidney or serious bleeding disorder).

21.5 Acute kidney injury 4827 In some areas of eastern and central Europe, there is a more severe form of hantavirus infection, which is similar to that seen in Asia. In Asia The Hantaan and Seoul viruses cause hantavirus disease in Asia: the former causes more severe illness, but both are considerably more dangerous that the Puumala hantavirus seen in Europe. A total of five phases of disease are recognized: • High fever and myalgias, followed by headache and severe ab- dominal/loin pain, often with an erythematous rash that may be- come petechial, also conjunctival haemorrhages • Severe hypotension • Gradual recovery of blood pressure, but associated with oliguria and renal failure with proteinuria and nonvisible haematuria— one-third of patients in this stage have significant problems with bleeding: gastrointestinal, intracerebral, or massive purpura (hence the terms epidemic or Korean haemorrhagic fever) • Polyuria • Convalescence Differential diagnosis is from severe leptospirosis and other causes of haemorrhagic fever found in Asia, including dengue and murine typhus. The diagnosis is made serologically. Treatment is supportive. Mortality is between 3 and 7%; survivors recover completely. ‘Haematological’ causes These are discussed in other chapters: haemolytic uraemic syn- drome (Chapter 21.10.6); idiopathic postpartum renal failure (Chapter 14.5); and plasma cell dyscrasias, immunoglobulin- based amyloidoses, fibrillary nephropathies, lymphomas, and leu- kaemias (Chapter 21.10.5). Hepatorenal syndrome The hepatorenal syndrome describes the presence of otherwise unexplained AKI in association with acute on chronic liver failure (see Chapter 15.22.5). It is a diagnosis of exclusion, in particular from AKI due to acute tubular necrosis in the context of intravas- cular volume depletion and/or sepsis. A large single-centre study of the causes of AKI in 463 patients with cirrhosis reported these to be infection (46% of cases), volume depletion (32%), hepatorenal syndrome (13%), and renal inflammatory disease (e.g. glomerulo- nephritis (9%)). In one study of 229 patients with cirrhosis and as- cites, it developed in 18% at 1 year and 39% at 5 years, and in another study it developed in 28 of 101 patients with acute alcoholic hepatitis. The mechanism of renal failure in hepatorenal syndrome is uncer- tain, but it is associated with splanchnic vasodilatation and markedly reduced renal perfusion. These may be precipitated by acute insults such as gastrointestinal bleeding or infection. Presentation is typic- ally with oliguria, an inactive urinary sediment, proteinuria less than 0.5 g/day, a very low urinary sodium concentration (<10 mmol/litre), and a rising serum creatinine. Based on speed of onset, two forms are described: type 1 with rapid deterioration (creatinine clearance falling to <20 ml/min or serum creatinine rising twofold to >221 μmol/litre (2.5 mg/dl) within 2 weeks); type 2 is less rapid. Diagnostic criteria are unsatisfactory because, as described earlier, they depend substantially on exclusion of other conditions. Hepatorenal syndrome may be characterized by ‘prerenal’ urinary biochemistry, in particular a very low urinary sodium concentration (<10 mmol/litre), but this is not a diagnostic criterion. Histologically, the kidneys are normal, a fact emphasized by the fact that they work normally if transplanted. The best treatment for hepatorenal syndrome is restoration of liver function. This may be achieved if the patient recovers from al- coholic or viral hepatitis, or from acute hepatic failure, or undergoes liver transplantation. Other measures that have been employed and may be helpful are manoeuvres designed to improve renal perfusion, including the combination of intravenous noradrenaline and intra- venous albumin, terlipressin (a vasopressin analogue), octreotide (a somatostatin analogue), and midodrine (a selective α1-adrenergic agonist). Transjugular intrahepatic portosystemic shunt procedures may provide short-term benefit. Whether and for how long to provide active treatment are diffi- cult decisions in the patient with hepatorenal syndrome whose liver shows no sign of improving and for whom there is no opportunity for liver transplantation. Prognosis is poor and there is significant risk of prolonging death rather than supporting life. A multicentre study in Canada reported outcomes of 472 patients with cirrhosis who required renal replacement therapy for AKI, 341 of whom were not listed and 131 were listed for a liver transplant. In the nonlisted group, median survival was 21 days for those diagnosed with hepatorenal syndrome and 85% of all patients had died by 6 months. The risk of hepatorenal syndrome can be reduced in patients with spontaneous bacterial peritonitis by administration of intravenous albumin in addition to antibiotics. A randomized trial has dem- onstrated reduced rates of hepatorenal syndrome with norfloxacin (400 mg daily) in selected patients with cirrhosis and ascites. A trial of pentoxifylline showed benefit in alcoholic hepatitis, but a system- atic review has not confirmed this. Urinary obstruction This is discussed in Chapter 21.17. FURTHER READING Abassi ZA, et al. (1998). Acute renal failure complicating muscle crush injury. Semin Nephrol, 18, 558–65. Ali T, et al. (2011). The changing pattern of referral in acute kidney injury. QJM, 104, 497–503. Allegretti AS, et al. (2018). Prognosis of patients with cirrhosis and AKI who initiate RRT. Clin J Am Soc Nephrol, 13, 16–25. Anderson SM, Park ZH, Patel RV (2011). Intravenous N-acetylcysteine in the prevention of contrast media-induced nephropathy. Ann Pharmacother, 45, 101–7. Ash SR (2001). Peritoneal dialysis in acute renal failure of adults: the safe, effective, and low-cost modality. Contrib Nephrol, 132, 210–21. Bagshaw SM, et al. (2008). 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