Dangerous hyperkalaemia, out of proportion to the degree of renal impairment, can occur in those treated with a combination of potassium-sparing diuretics and ACE inhibitors or angiotensin II receptor blockers.

Obstructive jaundice may be incriminated in the development of ARF when there is no other obvious cause, but the precise mechanism is unclear. Although the toxic effects of circulating endotoxin or bile have been held responsible for the renal haemodynamic disturbances observed in these patients, others have suggested that jaundice renders the kidneys more sensitive to ischaemia.

ARF is also common in hepatic failure. Although most cases are due to identifiable prerenal factors or to vasomotor nephropathy associated with hypotension, gastrointestinal haemorrhage or sepsis, in a few the mechanism is unclear. In decompensated cirrhosis, ARF is probably caused by a redistribution of renal blood flow, with a reduction in total flow and GFR occurring only as late events. This redistribution of flow may largely account for the intense sodium retention that occurs in cirrhosis, with hyperaldosteronism playing a less important role. The ability to handle a water load, concentrate urine and excrete hydrogen ions is also impaired in cirrhotics. ARF may then be precipitated by an episode of gastrointestinal bleeding, a sudden increase in ascites or overvigorous diuretic administration.

In critically ill patients, ARF commonly occurs in association with sepsis, severe sepsis, septic shock and multiple-organ dysfunction syndrome (MODS) (see Chapter 5). Perioperative ATN accounts for 20–25% of all cases of ARF occurring in hospital. Patients at risk include those with pre-existing renal impairment, hypertension, cardiac disease, peripheral vascular disease, diabetes mellitus, jaundice and advanced age.

In summary, therefore, although it has been suggested that renal cortical ischaemia is the main pathogenic event in ARF, it seems likely that in most cases more than one mechanism is involved and that the factors initiating the damage are not necessarily the same as those that perpetuate renal dysfunction. In the recovery phase renal function is restored by repair, regeneration and proliferation of renal parenchymal cells. Growth factors play an important role in this process.

**DIAGNOSIS AND INVESTIGATIONS**

(Table 13.3)

In critically ill patients, oliguria (urine output < 0.5 mL/kg per hour) is usually the first indication that renal function is impaired. The diagnosis is then confirmed by:

- a progressive rise in blood urea and creatinine levels;
- a metabolic acidosis;
- hyperkalaemia;
- salt and water retention.

Occasionally, an unexpected increase in plasma potassium concentration is the earliest sign of impaired renal function, particularly in the presence of extensive tissue injury.

Oligo/anuria is not, however, an essential prerequisite for the diagnosis of ARF, since when renal concentrating ability is reduced even a urine production of 2–3 L/day may not reflect a sufficiently high GFR to excrete the nitrogenous metabolic waste products, particularly if the patient is hypercatabolic. It is also important to appreciate that, in critically ill patients, alterations in circulating levels of antidiuretic hormone (ADH), aldosterone and atrial natriuretic factor (ANF) play an important role in the development of oliguria, as do the effects of positive-pressure ventilation, positive end-expiratory pressure (PEEP), fluid restriction and diuretics in those with respiratory failure (see Chapters 7 and 8). Anuria is suggestive of renal tract obstruction, although rarely it may be due to renal cortical necrosis, necrotizing glomerulonephritis or loss of vascular supply to the kidneys.

In all cases, and particularly if the patient is anuric or has intermittent complete anuria, bladder outflow obstruction must be excluded. This possibility should be suspected in patients with previous symptoms of prostatic enlargement and in those who have suffered recent trauma or surgery to the pelvic area. Examination may reveal an enlarged bladder. If there is any doubt, aseptic bladder catheterization should be performed or, if a urinary catheter is already in place, obstruction of the catheter should be excluded (bladder washout). It is usually advisable to obtain the assistance of a urologist and in those with trauma an ultrasound scan should be performed before catheterizing the bladder. Rectal and vaginal examinations should be performed and the external genitalia must be inspected.

<table>
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<th>Table 13.3 Investigations in acute renal failure</th>
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<tbody>
<tr>
<td>Urea, creatinine</td>
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<td>Sodium, potassium</td>
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<td>Plasma and urine osmolality</td>
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<td>Urine sodium and protein content</td>
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<td>Ultrasound scan of kidney</td>
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<tr>
<td>Renography</td>
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<tr>
<td>Renal arteriography</td>
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<td>High-dose intravenous urography</td>
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<td>Ureterography</td>
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<td>Renal biopsy</td>
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Anuria is an ominous sign in patients who have recently undergone surgery to the aorta in close proximity to the renal arteries. If loss of vascular supply to the kidneys is a serious possibility, then the implications for management are profound. An early contrast-enhanced computed tomography (CT) scan, perhaps followed by direct renal arteriography if no perfusion is shown, is indicated.

Once bladder outflow obstruction has been excluded, it is important to determine whether the patient has prerenal, intrarenal or postrenal failure.

The history can provide a clue to the aetiology and may establish whether there was any pre-existing renal impairment (e.g. long-standing diabetes, hypertension). Patients with markedly elevated plasma urea and creatinine concentrations who are not overtly symptomatic are more likely to have slowly progressive renal failure. Many critically ill patients will be unable to communicate, but relatives or close friends can be interviewed and documented case histories will often be available from the admitting team or referring hospital. It is important to establish whether there is any evidence of previous renal disorders (childhood nephrotic syndrome, haematuria, nocturia, renal colic, hypertension, failed medical examinations for insurance purposes or for entry into the armed forces) as well as to ask about recognized aetiological factors such as ingestion of NSAIDs (particularly in patients with arthritis or migraine), ‘mainlining’ of drugs, diabetes mellitus, and recent infections, surgery or trauma. The family history may suggest the possibility of polycystic disease. Finally, it is important to enquire about exposure to unusual chemicals or solvents at work or in the home and recent travel abroad.

Old case notes should be scrutinized for the results of previous urine testing (proteinuria, haematuria), urea and creatinine determinations and blood pressure recordings. Plain abdominal films, intravenous urograms or ultrasound examinations may also be available and can give an indication of previous kidney size and the presence of stones.

Recent notes may reveal an episode of hypotension (e.g. on the anaesthetic chart) or sepsis, as well as providing a record of drugs administered (look particularly for gentamicin, NSAIDs and contrast media).

**PRERENAL FAILURE**

In prerenal failure the excretory function of the kidneys is impaired by shock, hypovolaemia or dehydration; this causes an appropriate oliguria and a reduction in GFR, with maximal tubular reabsorption of salt and water. Usually proteinuria is absent and the urinary sediment unremarkable.

In general, blood urea rises more than creatinine and the urine is concentrated (osmolality > 500 mmol/L) with a high urea and low sodium content (< 20 mmol/L), and a low fractional excretion of sodium (FENa < 1%). In some cases, however, there may be a renal leak of sodium, in which case urinary sodium content may be higher than 30 mmol/L and oliguria is less marked or absent. In the absence of hypovolaemia, low urine sodium concentrations may also be seen with radiocontrast nephropathy, haemoglobinuria and vasculitis, as well as in those with hepatorenal syndrome or cardiac failure. Classically, in prerenal oliguria the urine: plasma ratios of osmolality, urea and creatinine are greater than 2, 30 and 15 respectively.

Unfortunately, in many intensive care patients, values for these biochemical indices are borderline or misleading, especially in non-oliguric renal failure, when diuretics, or osmotically active agents such as radiocontrast media, have been administered, and in those with pre-existing renal or hepatic disease, cardiac failure or electrolyte disturbances (particularly hypokalaemia). Also a raised urea/creatinine ratio may be a consequence of a high-protein diet, catabolism, gastrointestinal bleeding, steroid therapy and a reduced body mass.

Importantly, ARF secondary to rhabdomyolysis is associated with a low urea-to-creatinine ratio because creatine released from injured muscle leads to a disproportionate increase in plasma creatinine concentration. A low urea-to-creatinine ratio may also be the result of reduced urea synthesis due to malnutrition or liver disease, or a consequence of increased elimination of urea due to an increased GFR, as occurs in pregnancy. Biochemical indices are, therefore, rarely of value and the diagnosis can only be made on the basis of a clinical assessment of the state of hydration (oedema, neck veins, blood pressure, postural hypotension) and the response to a volume challenge, guided as necessary by measurements of central venous pressure (CVP) and, in some cases, more complex haemodynamic monitoring.

**URINARY TRACT OBSTRUCTION**

Once prerenal failure has been excluded, the most immediate priority is the exclusion or identification of urinary tract obstruction. In most patients, ultrasound scanning can reliably identify obstruction, as well as providing a reasonable estimate of kidney size, and is the most practical and useful imaging technique in intensive care patients. Enlarged kidneys in a patient with ARF suggest obstruction, amyloidosis, renal infiltration (e.g. lymphoma) or TIN. In some cases of obstructive uropathy, however, dilatation of the urinary tract does not occur, for example when malignancy is the cause of the obstruction, when the patient is severely dehydrated, in those with retroperitoneal fibrosis and in acute obstruction. If ultrasound is inconclusive, contrast-enhanced CT scanning or high-dose intravenous urography provides the same information and very occasionally may define the site of the obstruction. Usually, however, when obstruction is detected, antegrade or retrograde ureterography is necessary to define the site. Obstruction requires skilled urological assessment with a view to urgently re-establishing free drainage of urine.

**ACUTE RENAL FAILURE**

The diagnosis of intrinsic ARF is suggested by demonstrating that urine osmolality is similar to that of plasma (< 350 mmol/l), that the urinary sodium concentration is high (> 20–50 mmol/l), the FENa is above 2% and that the urinary
potassium concentration is low (< 10 mmol/l). There is some evidence to suggest that serum cystatin may be an early and reliable marker of the development of ARF in critically ill patients (Herget-Rosenthal et al., 2004). Other biomarkers which may prove to be useful for the early diagnosis of ARF include urinary interleukin-18 and tubular enzymes, such as the intestinal form of alkaline phosphatase, N-acetyl-β-glucosaminidase, alanine aminopeptidase and neutrophil gelatinase-associated lipocalin (NGAL) (Mishra et al., 2005).

Proteinuria is usually present and the urine contains casts composed of tubule epithelial cells and/or cellular debris. The differential diagnosis then includes:

- ATN;
- glomerular lesions (acute glomerulonephritis, vasculitis);
- cortical necrosis;
- TIN;
- renal vascular lesions;
- an acute exacerbation of chronic renal disease.

Renal size must be determined since small kidneys are indicative of underlying chronic renal disease, although renal size may be maintained in some chronic disease such as diabetes. An ultrasound scan may reveal the size of the kidneys or even suggest polycystic disease. The diagnosis of rhabdomyolysis is supported by an elevated serum creatine phosphokinase level and by detecting myoglobin in the urine. The serum potassium is usually markedly elevated and there may be hypocalcaemia due to a shift of calcium into injured muscle (see Chapter 10).

Glomerular disease

The possibility that ARF is due to a glomerular lesion should be considered, particularly when there are extrarenal signs such as:

- skin lesions indicative of systemic vasculitis;
- arthritis;
- neurological manifestations (e.g. mononeuropathies);
- pulmonary involvement.

Hypertension is usual in these cases. Serum complement levels may be reduced and, in some, circulating immune complexes are identified. Examination of the urine may reveal red cell casts and proteinuria, whereas in vasomotor nephropathy the urinary sediment will contain only tubular cells with a few granular casts. Urine and blood cultures are essential to exclude infection. Ultrasound examination may reveal increased cortical echogenicity, although this is a non-specific finding. If the presentation suggests the possibility of a treatable lesion, renal biopsy may be indicated. There is, however, a significant incidence of complications with this procedure, particularly haemorrhage, and the risks should be weighed against the likely benefits.

When glomerular disease presents as ARF, it is usually due to an acute process such as RPGN or a systemic disease such as Wegener’s granulomatosis, PAN, SLE or Goodpasture’s syndrome. Goodpasture’s syndrome should be suspected when there is pulmonary involvement with haemorrhage; the diagnosis can be confirmed by demonstrating linear deposits of immunoglobulin G (IgG) along the glomerular basement membrane and by identifying circulating antiglomerular basement membrane antibody. Pulmonary involvement, sometimes with haemorrhage, is also a feature of Wegener’s disease and SLE but is very uncommon in PAN. Antineutrophil cytoplasmic antibodies (ANCA) are present in more than 90% of patients with Wegener’s granulomatosis.

Renal cortical necrosis

Renal cortical necrosis is extremely rare in adults, but usually presents as ARF and cannot normally be distinguished from vasomotor nephropathy in the acute stage. The aetiological factors are often the same and include:

- severe shock;
- major surgery;
- transfusion reactions;
- infections;
- burns.

Cortical necrosis occurs particularly in association with obstetric disasters, especially later in pregnancy. It has been suggested, therefore, that cortical necrosis occurs most often in those with a hypercoagulable state in whom development of DIC may cause particularly severe renal ischaemia. Cortical necrosis may simply be a more severe form of ATN with less chance of recovery, and should be suspected if oliguria is prolonged. The diagnosis is likely if the kidney size is found to be decreasing: cortical calcification, which appears in approximately half the patients after about 6 weeks, is virtually diagnostic. In such cases, a renal biopsy may be performed to confirm the diagnosis.

Acute interstitial nephritis

Acute interstitial nephritis is suggested by:

- a rash;
- fever;
- joint involvement;
- eosinophilia (not invariable);
- raised serum IgE levels.

Large numbers of eosinophils may be identified in the urine. Renal biopsy confirms the diagnosis.

Renal vascular lesions

Renal vascular lesions present as sudden oliguria, or often complete anuria, accompanied by hypertension, macroscopic haematuria and loin pain. The diagnosis can be confirmed by radioisotope scan, renal vascular Doppler studies, CT scan or renal arteriography. The latter will be required to define the site of the lesion.
CONSENSUS DEFINITIONS

It has been suggested that the absence of consensus definitions for ARF, as have been applied to acute lung injury, for example, has hampered research and progress in this field (Bellomo et al., 2001). These investigators have therefore proposed definitions to cover the spectrum of renal injury, the concept being similar to that applied to sepsis (see Chapter 5). Recently the Acute Dialysis Quality Initiative group proposed the RIFLE system in which ARF is classified into three categories of severity (risk, injury and failure) and two clinical outcome categories (loss and end-stage renal disease) (Table 13.4). This system seems to be a valid predictor of clinical outcomes (Herget-Rosenthal et al., 2004).

CLINICAL COURSE AND MANAGEMENT
(Tables 13.5 and 13.6)

Outside hospital ARF typically presents as isolated, single-organ disease, which, provided that the cause is readily identified and treated, can have a good prognosis. Most cases occur in hospital, however, and ARF complicates around 5% of all hospital admissions and up to 25% of admissions to intensive care depending on the patient population and criteria for definition. Although the development of ARF in hospitalized patients may occasionally be attributable to a single identifiable event such as hypotension or drug toxicity, it is usually associated with multiple insults, especially hypovolaemia, hypotension and nephrotoxic drugs, frequently in the context of multiple-organ failure and sepsis. The outcome in this latter category of patient is often poor, particularly in those with respiratory failure. Moreover there is now good evidence that the development of ARF is strongly associated with an increased risk of death, independent of the underlying condition and comorbidities (Levy et al., 1996).

Prevention of ARF is therefore a fundamental aspect of intensive care practice. This entails:

- early identification of those at risk, including:
  - the elderly;
  - diabetics;
  - hypertensives;
  - patients with atherosclerosis, chronic heart failure or hepatic cirrhosis;
  - patients receiving NSAIDs, cyclooxygenase-2 inhibitors, ACE inhibitors, angiotensin II receptor antagonists, amphotericin, gentamicin;
  - patients given radiocontrast agents;
  - patients with pre-existing renal impairment (Fig. 13.1) or renal artery stenosis;
  - optimization of renal perfusion (Chapter 5);
  - restore intravascular volume;
  - maintain MAP > 70 mmHg (or > 80–90 mmHg in those with impaired autoregulation);
  - maintain cardiac output with vasopressors/inotropes as indicated;
  - avoid vasoconstriction;
  - careful maintenance of crystalloidal balance (Chapter 11);
  - aggressive treatment of sepsis (Chapter 5);
  - the avoidance of nephrotoxic drugs (gentamicin is less toxic when administered as a single daily dose);
  - the avoidance of drugs that impair autoregulation of renal blood flow (NSAIDs, ACE inhibitors, angiotensin II receptor blockers);
  - allopurinol to decrease uric acid synthesis in patients with leukaemia or lymphoma who are prone to uric acid nephropathy, particularly following chemotherapy;
  - constant vigilance for the early signs of impaired renal function, followed by immediate corrective measures when required, is also essential. In some circumstances, the use of specific preventive therapy is warranted (see later in this chapter).

PRERENAL FAILURE

Prerenal failure should be treated by optimizing the circulating volume, replacing fluid and electrolyte deficits, and restoring the blood pressure. If cardiac output and blood pressure remain low despite volume expansion, inotropes and vasopressors should be administered as indicated, the objective being to avoid afferent arteriolar constriction and efferent vasodilation while maintaining an adequate renal

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<td>Failure</td>
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GFR, glomerular filtration rate.
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