General Internal Medicine for the Physician

Acute renal failure

Paul A Glynne MRCP

Liz Lightstone FRCP

Renal Section, Division of Medicine, Imperial College School of Medicine, Hammersmith Hospital, London

Clin Med JRCPL 2001;**1**:266–73

The treatment of patients with acute renal failure (ARF) and its life-threatening metabolic complications is one of the most challenging areas of acute medicine. Given its high incidence and diverse aetiologies, ARF frequently presents to physicians working in a wide range of specialties outside nephrology. With this in mind, the following review discusses the general approach to patients presenting with ARF and highlights key management principles. This vast subject is reviewed in greater detail elsewhere[1,2].

Key Points

- Acute renal failure (ARF) is usually associated with oliguria (urine output <400 ml/day), increased plasma urea, creatinine and potassium concentrations, acidosis, and ultimately fluid overload
- In-hospital ARF is most commonly caused by acute tubule necrosis resulting from multiple nephrotoxic insults such as hypotension, sepsis and nephrotoxic drugs
- In at-risk patients (elderly, diabetics and those with vascular disease, particularly after exposure to angiotensin-converting enzyme inhibitors or radiocontrast), optimise intravascular volume and avoid nephrotoxic drugs
- Discuss all cases of ARF with a nephrologist
- Exclude urinary tract obstruction in all patients presenting with ARF
- Early recognition of rapidly progressive glomerulonephritis (haematuria, urinary red cell casts and features of systemic inflammation), an important cause of ARF developing outside hospital, is crucial since early treatment may prevent the development of end-stage renal failure
- In established ARF, the immediate priority is to make the patient safe by treating hyperkalaemia and fluid overload
- Urgent dialysis is indicated in the presence of severe, refractory hyperkalaemia, profound metabolic acidosis, pulmonary oedema and severe uraemia (encephalopathy, pericarditis or bleeding)

Definition

ARF can be defined as an abrupt, sustained rise in serum urea and creatinine due to a rapid decline in glomerular filtration rate (GFR), leading to loss of normal water and solute homeostasis, and life-threatening metabolic sequelae. This occurs over hours to days, although ARF may develop on a background of chronic renal failure (CRF), so-called acute-on-chronic renal failure. The incidence of severe ARF (creatinine >500 μmol/l) is approximately 140 per million population per year[3]. Outside hospital, ARF typically presents as isolated, single-organ disease which, if the cause is readily identified and treated, may have a good prognosis. However, most cases of ARF occur in hospital, complicating around 5% of all medical and surgical admissions[4], and are usually associated with multiple nephrotoxic insults, especially hypovolaemia, hypotension and nephrotoxic drugs. Despite the advent of renal replacement therapies (RRT), in-hospital mortality attributable to ARF remains high (up to 50%)[5], probably reflecting the increasing number of critically ill patients undergoing continuous renal replacement therapy (CRRT) in the intensive care unit (ICU).

Oliguric ARF, defined as a reduction in urine output to less than 400 ml/day[6], leads to a rise in plasma urea, creatinine and potassium concentration, acidosis, and ultimately fluid overload. Approximately 20% of patients develop non-oliguric ARF, most commonly in the context of aminoglycoside and radiocontrast nephrotoxicity, which may be associated with a lower risk of requiring RRT[7,8]. Conversion of oliguric ARF to a non-oliguric state is thus a major objective of therapy, with prevention of ARF the primary goal wherever possible.

Aetiology

ARF is most often related to ischaemic (50%) or nephrotoxic (35%) injury to the kidney, frequently occurring as part of a multisystem disorder such as severe sepsis or trauma[5]. Early recognition of potentially reversible causes of ARF makes it possible to start treatment early, and may avoid the higher morbidity and mortality associated with established ARF.

It is helpful to consider the primary aetiology of ARF according to the underlying pathophysiology (Table 1). The causes are conveniently categorised as:

- pre-renal ARF
- intrinsic ARF (acute tubule necrosis (ATN) and other diseases of the renal parenchyma)
- post-renal ARF.

Pre-renal acute renal failure

Pre-renal ARF describes the reversible fall in GFR that follows renal hypoperfusion below the autoregulatory limit, predominantly secondary to hypotension and hypovolaemia. Autoregulation is the ability of the renal circulation to maintain relatively constant blood flow over changes in a mean arterial pressure (MAP) range of about 70–180 mmHg. (MAP is calculated as 1/3 systolic blood pressure (BP) + 2/3 distolic BP; BP limits for autoregulation are approximately 90/70 and 260/140 mmHg.) This prevents major changes in renal blood flow due to MAP fluctuations, and prevents excessive alterations in salt and water excretion by avoiding significant changes in GFR. Therefore, in a patient without pre-existing hypertension, a MAP above 70 mmHg is required to maintain normal renal function. If the MAP is below 70 mmHg, virtually no adaptation to the effects of hypotension is possible and GFR falls. Restoration of renal perfusion (eg by restoring intravascular volume) will reverse the decline in GFR. If untreated, however, prolonged renal hypoperfusion leads to post-ischaemic ATN.

Intrinsic acute renal failure

Intrinsic ARF is caused by diseases affecting the tubulointerstitium, glomerulus or renal vasculature.

Acute tubule necrosis. Most cases of ARF in hospital are due to ATN, a histological diagnosis that describes the renal morphological changes common to several ARF aetiologies[9], particularly ischaemia, sepsis and nephrotoxic agents such as angiotensin-converting enzyme (ACE) inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs). Renal injury in ATN is predominantly confined to the outer medullary tubule segments: the S3 segment of the proximal tubule and the thick ascending limb of the loop of Henle. Despite normal renal blood flow of about 1,200 ml/min (equivalent to ca 25% of the resting cardiac output), the proximal tubule is particularly susceptible to ischaemic damage. This is because of the high energy requirements of S3 segment proximal tubule cells and the low oxygen tension (PO_2 10–20 mmHg) of the outer renal medulla resulting from low medullary blood flow and the countercurrent exchange of oxygen[10].

ATN results from either prolonged renal hypoperfusion (post-ischaemic ARF), representing the more severe end of the spectrum of pre-renal disorders, or direct tubule epithelial cell injury (see Table 1). Hypoxia induces disruption of the tubule cell cytoskeleton, loss of cell polarity, dissolution of integrin-dependent cell matrix adhesion, and shedding of viable, necrotic and apoptotic tubule cells[11,12]. Tubule cell production of the signalling molecule nitric oxide plays a major pathogenic role in cell shedding[13], leading to intratubular obstruction and a fall in GFR.

Acute tubulointerstitial nephritis. Acute drug-induced tubulointerstitial nephritis (TIN) is another common cause of intrinsic ARF. The most frequently encountered precipitating agents are penicillins, sulphonamides and NSAIDs, although many other drugs have been reported to cause acute TIN.

Rapidly progressive glomerulonephritis. Glomerular causes of ARF are predominantly those associated with the syndrome of rapidly progressive glomerulonephritis (RPGN). RPGN is

Table 1. The aetiology of acute renal failure.

Pre-renal acute renal failure (55–60% of cases)	
Hypovolaemia	Haemorrhage, burns, pooling of fluid (pancreatitis, crush injury, intestinal obstruction), GI fluid loss (enteric fistulae/tube drainage, diarrhoea, vomiting), renal losses (glycosuria, post-obstructive diuresis, diuretics)
Hypotension	Cardiogenic shock, distributive shock (sepsis, anaphylaxis)
Renal hypoperfusion	Renal vasoconstriction (especially NSAIDs and COX2 inhibitors in elderly hypovolaemic patients, radiocontrast agents, endotoxin), MAP 80–90 mm Hg + impaired autoregulation (elderly patients, diabetes, atherosclerosis, bilateral renal artery stenosis + ACE inhibitor/angiotensin II receptor antagonist), aortic aneurysm affecting renal vessels, renal artery thrombosis
Oedematous states	Chronic heart failure, hepatic cirrhosis, hepatorenal syndrome
Intrinsic acute renal failure (35–40% of cases)	
ATN	Ischaemia (secondary to pre-renal ARF), direct tubule epithelial cell toxicity (aminoglycosides, cisplatin, amphotericin B, radiocontrast agents (especially in hypovolaemic patients), myoglobinuric ARF (secondary to rhabdomyolysis), sepsis, heavy metal poisoning
Disease/occlusion of renal arteries	Vasculitis, atheroemboli, cholesterol emboli, infarction
Disease of glomeruli/ arterioles	RPGN, myeloma, thrombotic microangiopathy, malignant hypertension, microscopic polyarteritis, scleroderma, SLE
Acute TIN	Drug-related/allergic, parainfectious, paraneoplastic
Post-renal acute renal failure (<5% of cases)	
	Calculi, sloughed papillae, carcinoma, retroperitoneal disease (carcinomatous infiltration, idiopathic fibrosis, lymphoma), bladder carcinoma, acutely neurogenic bladder, prostatic enlargement, urethral stricture/stenosis, blocked catheter

ACE = angiotensin-converting enzyme; ARF = acute renal failure; ATN = acute tubule necrosis; COX = cyclo-oxygenase; GI = gastrointestinal; MAP = mean arterial pressure; NSAID = non-steroidal anti-inflammatory drug; RPGN = rapidly progressive glomerulonephritis; SLE = systemic lupus erythematosus; TIN = tubulointerstitial nephritis.

an important cause of ARF developing outside hospital; it should always be considered even when features of systemic inflammation are not present (Table 2). The diagnosis of RPGN must not be missed, since early treatment may prevent the development of end-stage renal failure[14].

Myeloma. Myeloma is a relatively common cause of ARF presenting from the community, particularly in older patients. In this situation, ARF can arise from hypercalcaemia, cast nephropathy, hyperuricaemia, hyperviscosity syndrome, light chain deposition or amyloid. Apart from measures to correct volume status, such patients require joint renal and haematological care to treat myeloma promptly in the hope of altering patient and renal survival.

Vascular causes. Vascular causes of ARF are uncommon but require immediate therapy to avoid permanent loss of renal function. Renal artery occlusion may occur secondary to aortic dissection or from arterial embolism. In patients with severe nephrotic syndrome, renal vein thrombosis may cause a sudden deterioration in renal function, often accompanied by loin pain and haematuria. Microvascular occlusion is another major cause of ARF, typically from a thrombotic microangiopathy such as those associated with pre-eclampsia, haemolytic uraemic syndrome, scleroderma and malignant hypertension.

Post-renal acute renal failure

Renal failure secondary to urinary obstruction, so-called obstructive uropathy, typically presents as chronic renal impairment. In contrast, renal tract obstruction is an uncommon cause of ARF, accounting for less than 5% of cases. However, a rapid diagnosis of obstruction by clinical and ultrasound examination is imperative, as early intervention (eg bladder catheterisation,

Table 2. Acute renal failure: clinical features and laboratory investigations.

Diagnosis	Clinical features/ aetiology	Important investigations	Treatment principles
ATN	Hypotension, hypovolaemia, nephrotoxins	Mainly a clinical diagnosis Urinary epithelial cell casts	Fluid resuscitation, treat primary aetiology, withdraw nephrotoxins
RPGN*	Fevers, arthralgia, rash, splinter haemorrhages, scleritis, neuropathy Lung haemorrhage (GBM, WG, CSS, SLE, MEC, HSP) Asthma & nasal polyps (CSS) Epistaxis, granulomas, nasal collapse & deafness (WG)	Dipstick +ve blood, +ve protein; red cell casts Anti-GBM Ab (GBM) C-ANCA (WG, MP) P-ANCA (MP, CSS) Anti-dsDNA/C1q Ab (SLE) ↓C3 (SLE, IE) ↓C4 (SLE) Cryoglobulins & ↓C4 (MEC)	Immunosuppressive drug (corticosteroids, cyclophosphamide) – plasma exchange may be indicated (**not** for IE)
Acute TIN	Fever, rash and arthralgias ~ 2 weeks following drug exposure	Urinary white cell casts, eosinophiluria – eosinophilia	Withdraw offending agent Role for corticosteroids?
Myeloma	Hypercalcaemia, cast nephropathy, amyloid, light chain deposition, NSAIDs, hyperviscosity, hyperuricaemia	Bence-Jones proteinuria Monoclonal band on serum protein electrophoresis, immuneparesis	Treatment according to cause (eg hydration, chemotherapy, plasma exchange)
Rhabdomyolysis	Commonly follows crush injuries (eg related to trauma, loss of consciousness, alcohol, recreational drugs)	Brown urine, dipstick +ve for blood, but no blood on microscopy; myoglobinuria Muscle cell lysis leads to –creatine kinase, $-K^+$, $-PO4^{2-}$	Hydration – alkaline diuresis (if adequate urine output) Dialysis often required until recovery
HUS	Diarrhoea (D) +ve (*Escherichia coli* O:H 157) or D-ve (eg due to mitomycin, quinine, cyclosporin, malignant hypertension)	Microangiopathic haemolytic anaemia Thrombocytopenia Normal coagulation	Plasma exchange with fresh frozen plasma or cryo-poor supernatant
Cholesterol embolisation	Atheromatous vascular disease Precipitated by angiography, surgery or anticoagulation Rash ('trash foot') ± retinal cholesterol deposits Mimics RPGN	Eosinophilia ↓C3	Consider 'statins'

*Causes of rapidly progressive glomerulonephritis (RPGN) include anti-glomerular basement membrane disease (GBM, Goodpasture's disease), Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS), microscopic polyangiitis (MP), systemic lupus erythematosus (SLE), mixed essential cryoglobulinaemia (MEC), Henoch-Schonlein purpura (HSP) and infective endocarditis (IE).

Ab = antibody; ANCA = anti-neutrophil cytoplasmic antibody; ATN = acute tubule necrosis; C = complement component; HUS = haemolytic uraemic syndrome; NSAID = non-steroidal anti-inflammatory drug; TIN = tubulointerstitial nephritis.

nephrostomy) relieves the obstruction, frequently corrects oliguria, and significantly reduces the chance of developing intrinsic ARF.

Prevention

Given the high mortality associated with established in-hospital ARF, every effort should be made to prevent the development of this complication.

Identification of at-risk patients

Identification of patients at greatest risk of ARF makes preventive measures possible. The main risk factors for pre-renal ARF are listed in Table 1, with the addition of pre-existing renal impairment which may be present before the plasma creatinine concentration rises above the normal range. This occurs because the relationship between plasma creatinine and creatinine clearance (CrCl) (a measure of GFR) is hyperbolic rather than linear (Fig 1). Therefore, a reduction in GFR from 60 ml/min to 30 ml/min will double the plasma creatinine, whereas a reduction from 120 ml/min to 60 ml/min may result in only a minor increase in plasma creatinine. In practice, this means that a small rise in plasma creatinine, for example from 90 µmol/l to 120 µmol/l, may indicate a marked fall in GFR and should alert the clinician to the possibility of significant renal impairment. Plasma creatinine is influenced both by diet and by drugs that compete for tubular secretion of creatinine (eg trimethoprim, cimetidine, amiloride, spironolactone). In addition, the interpretation of plasma creatinine depends on the patient's size, sex and age. This relationship is expressed by the Cockcroft-Gault equation for CrCl (ml/min):

$$\frac{(140 - \text{age in years}) \times \text{weight in kg}}{\text{serum creatinine (µmol/l)}}$$

(correction for males × 1.23, females × 1.04).

Thus, a plasma creatinine of 110 µmol/l in a 45 year old man weighing 80 kg corresponds to a CrCl of about 85 ml/min, and the same plasma creatinine in an 80 year old woman weighing 45 kg to a CrCl of about 25 ml/min.

Patients with diabetes, especially those with microalbuminuria, proteinuria, hypertension or vascular disease, particularly those exposed to ACE inhibitors or radiocontrast, and the elderly are all highly susceptible to pre-renal insults, and are therefore at increased risk of ARF. These patients often have impaired autoregulation (90–180 mm Hg), and may therefore suffer a fall in GFR at a MAP of 80–90 mmHg rather than below 70 mmHg. This has important implications for the haemodynamic and fluid management of these patient subgroups (see below).

Preventative treatment

Having identified at-risk patients, renal function and fluid balance should be closely monitored. The key preventative strategies include:

- optimising renal perfusion
- maintaining adequate diuresis
- avoiding nephrotoxic agents.

Renal perfusion depends on adequate MAP and intravascular volume. Clinical assessment of intravascular volume status includes pulse rate, jugular venous pressure, postural BP, daily weight measurement, and careful charting of fluid balance. When the clinical evaluation is difficult, invasive central venous pressure (CVP) monitoring aids assessment of intravascular volume and can guide fluid replacement. A reduction in intravascular volume, manifest by hypotension/postural hypotension, tachycardia, low jugular venous pressure, weight loss and oliguria leads to a fall in renal perfusion and oliguria, as salt and water are reabsorbed. Restoration of intravascular volume with fluid replacement is the single most important therapeutic manoeuvre that prevents progression from pre-renal to established ARF.

When hypovolaemia and oliguria are clinically apparent (eg haemorrhage, burns), intravenous (IV) fluid (eg blood, colloid or crystalloid, depending on the patient's clinical state) should be rapidly infused to maintain a MAP above 70 mmHg (or >80–90 mmHg in patients with impaired renal autoregulation), with the rate of infusion directed by the clinical response. However, oliguria often occurs with few or no clinical signs of hypovolaemia. In this situation, a fluid challenge is useful to help assess intravascular volume. Using CVP monitoring, 250 ml fluid boluses (colloid or crystalloid) should be given over 15 minutes until there is a sustained rise in CVP. In the absence of CVP monitoring, a rapid improvement in BP, tachycardia or urine output confirms hypovolaemia and would prompt a further fluid challenge. Following restoration of intravascular volume, fluid input should equal urine output, with additional fluids administered to cover insensible losses (~500 ml/day).

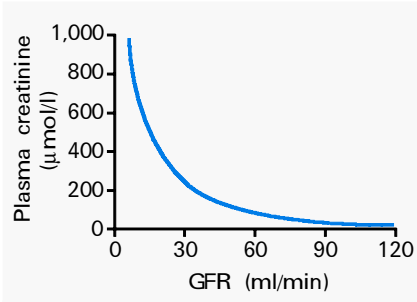


Fig 1. The relationship between plasma creatinine and glomerular filtration rate (creatinine clearance)

If MAP remains below 70 mmHg despite adequate fluid resuscitation, as determined by CVP monitoring (eg in cardiogenic or septic shock), transfer to a high dependency unit may be necessary for more invasive monitoring (eg oesophageal Doppler, Swan-Ganz catheterisation) and inotropic support.

If pre-renal oliguria persists after an adequate MAP (>70 mmHg or 80–90 mmHg in patients with pre-existing hypertension) has been achieved, it is likely that the patient has developed established ATN. Diuretics are often used in this setting to promote a diuresis and convert an oliguric state to a non-oliguric state. This may improve renal outcome[8], but there is no evidence from human studies that loop diuretics (furosemide), osmotic diuretics (mannitol) or natriuretics (dopamine) prevent or alter the course of ARF[15]. Loop

diuretics may help in allowing less fluid restriction in oliguric ATN, and can be useful in patients with oliguric ARF and impending fluid overload, especially when dialysis facilities are not immediately available. Before administering any diuretic, however, it is imperative that intravascular volume is adequate as diuresis in a hypovolaemic patient will further reduce renal perfusion and exacerbate renal injury. Furosemide may be administered as an IV bolus dose of 250 mg over 30 minutes. If oliguria persists following an initial bolus, there is no advantage in giving further furosemide (it is ototoxic in high doses) and the patient should be referred for RRT.

Investigation and diagnosis

The diverse aetiology of ARF often necessitates the use of a range of laboratory investigations to aid diagnosis and guide therapy, important examples of which are shown in Table 2. A standard clinical approach should be adopted for all patients presenting with ARF[2] and the following key issues addressed:

1 *Establish whether acute renal failure is truly acute, or due to acute-on-chronic renal failure*

The medical history may indicate whether patients are likely to have pre-existing renal impairment (eg long-standing diabetes, hypertension). If this is not apparent, it may be possible to obtain previous creatinine measurements from either the general practitioner or old case notes. A normal haemoglobin concentration in patients presenting with renal failure does not discriminate between ARF and CRF. Causes of anaemia in ARF include thrombotic microangiopathy, haemorrhage and disseminated intravascular coagulation. Patients with CRF generally adapt to their biochemical and osmotic disturbances. Therefore, patients with markedly elevated plasma urea (>50 mmol/l) or creatinine (>1,000 μmol/l) concentrations who are not overtly symptomatic are more likely to have slowly progressive renal failure. Small renal size on ultrasound examination reflects chronic renal impairment, although renal size may be maintained in chronic diseases such as diabetes. Enlarged kidneys and ARF suggest a diagnosis of renal tract obstruction, amyloidosis, renal infiltration (eg lymphoma) or TIN.

Patients may develop ARF on a background of chronic renal dysfunction, due either to exacerbation of an underlying renal disease (eg systemic lupus erythematosus, vasculitis) or to unrelated renal insults (eg hypovolaemia, sepsis, nephrotoxins).

2 *Exclude renal tract obstruction*

Absolute anuria is suggestive of renal tract obstruction, although rarely can be secondary to renal cortical necrosis or necrotising glomerulonephritis. Clinical examination may demonstrate a distended bladder in patients with urinary retention, confirmed by the drainage of a large residual urine volume following bladder catheterisation. Renal tract obstruction should be excluded by renal ultrasonography in all cases. Occasionally, obstructive ARF occurs in the absence of a non-dilated upper renal tract, particularly in the presence of renal tract malignancy. In these cases, serial ultrasound scans, computed tomography scanning or nuclear scintigraphy may reveal the underlying obstruction.

3 *Ensure patients are intravascularly volume replete*

The clinical assessment of intravascular volume has been discussed. Renal hypoperfusion often results in a disproportionate increase in the plasma urea:creatinine ratio, as urea is re-absorbed passively along with sodium and water (unlike creatinine, which is not re-absorbable). The urea:creatinine ratio must be interpreted with caution as a raised ratio may also be produced by:

- a high protein diet
- increased catabolism (eg post-surgery, infection)
- gastrointestinal bleeding
- corticosteroid therapy
- tetracycline
- a reduction in the plasma creatinine concentration due to reduced body muscle mass.

Importantly, myoglobinuric ARF secondary to rhabdomyolysis is associated with a low urea:creatinine ratio because creatine, released as a result of muscle injury, leads to a disproportionately high plasma creatinine concentration. A low urea:creatinine ratio also results from suppressed urea synthesis due to malnutrition or liver disease, or from increased urea elimination due to an elevated GFR (eg pregnancy).

Plasma and urine biochemistry can help to distinguish pre-renal ARF from ATN. The physiological response to volume depletion (ie pre-renal ARF) is tubule reabsorption of salt and water. This increases intravascular volume, resulting in appropriate oliguria, high specific gravity on urine dipstick testing, low urine sodium concentration (usually <20 mmol/l), high urine osmolality (>50 mosmol/kg), and low fractional excretion of sodium (FENa >1%) (FENa = sodium clearance/creatinine clearance). This mechanism is disrupted in ATN, primarily due to medullary ischaemia, with loss of tubule responsiveness to antidiuretic hormone. Urinary sodium concentration is usually above 40 mmol/l and FENa above 2%, with osmolality similar to that of plasma (<350 mosmol/kg). In the absence of hypovolaemia, low urine sodium concentrations may also be seen with radiocontrast nephropathy, haemoglobinuria and vasculitis, and also in patients with the hepatorenal syndrome or cardiac failure. A very low urinary sodium (<10 mmol/l) may help to confirm a diagnosis of hepatorenal syndrome.

These biochemical tests are of no value if the patient has received diuretics or osmotically active agents such as radiocontrast. In practice, this does not alter the immediate clinical management which is the same for both pre-renal ARF and ATN: that is, optimisation of intravascular volume and avoidance of fluid overload. During the diuretic recovery phase of ARF (see below) measurement of urinary sodium and potassium can be useful to guide appropriate electrolyte replacement.

4 *Exclude a major vascular occlusion*

ARF secondary to an acute renal vascular

occlusion is usually clinically apparent. Patients often complain of loin pain, macroscopic haematuria, and they may be completely anuric. Renal vascular Doppler studies or angiography will confirm the diagnosis.

5 *Determine whether parenchymal renal disease other than acute tubule necrosis is present*

Intrinsic renal disease other than ATN must be excluded in all patients with ARF. The importance of early recognition of RPGN has been discussed. The medical history may suggest multisystem disease, and physical examination can be informative (eg skin rashes of systemic vasculitis) but RPGN can present in isolation. Intrinsic parenchymal renal disease is commonly associated with increased renal cortical echogenicity on ultrasound examination, although this is a non-specific finding and does not distinguish between different intrinsic disease aetiologies. Urine dipstick testing and microscopy are essential to exclude an inflammatory renal disease. Haematuria, dysmorphic red blood cells, with or without red cell casts, in the urinary sediment are found in RPGN. Urinary eosinophils suggest drug-induced interstitial nephritis. All ARF associated with proteinuria and/or haematuria warrants prompt referral to a nephrologist, blood investigations to identify underlying autoimmune disease/vasculitis, and usually renal biopsy to determine the diagnosis. Urine and blood cultures are mandatory to exclude infection.

If the clinical history, examination and urinary sediment are not suggestive of active renal disease, obstruction has been excluded, renal function was previously normal and there are adequate clinical reasons for ATN to be present, further investigations to determine the cause of ARF are unnecessary.

Treatment principles

The initial treatment of all patients presenting with ARF requires optimisation of fluid balance and avoidance of nephrotoxic drugs (as described for prevention of ARF in at-risk patients). In cases of pre-renal ARF or non-oliguric ATN, this may be sufficient to reverse renal failure and obviate the need for RRT in oliguric ATN. If established ARF develops, therapy is directed at:

- making the patient safe, instituting rapid treatment of life-threatening metabolic disturbances secondary to ARF, irrespective of cause
- initiating RRT when appropriate
- general supportive measures
- therapeutic interventions targeted at the primary aetiology (Table 2).

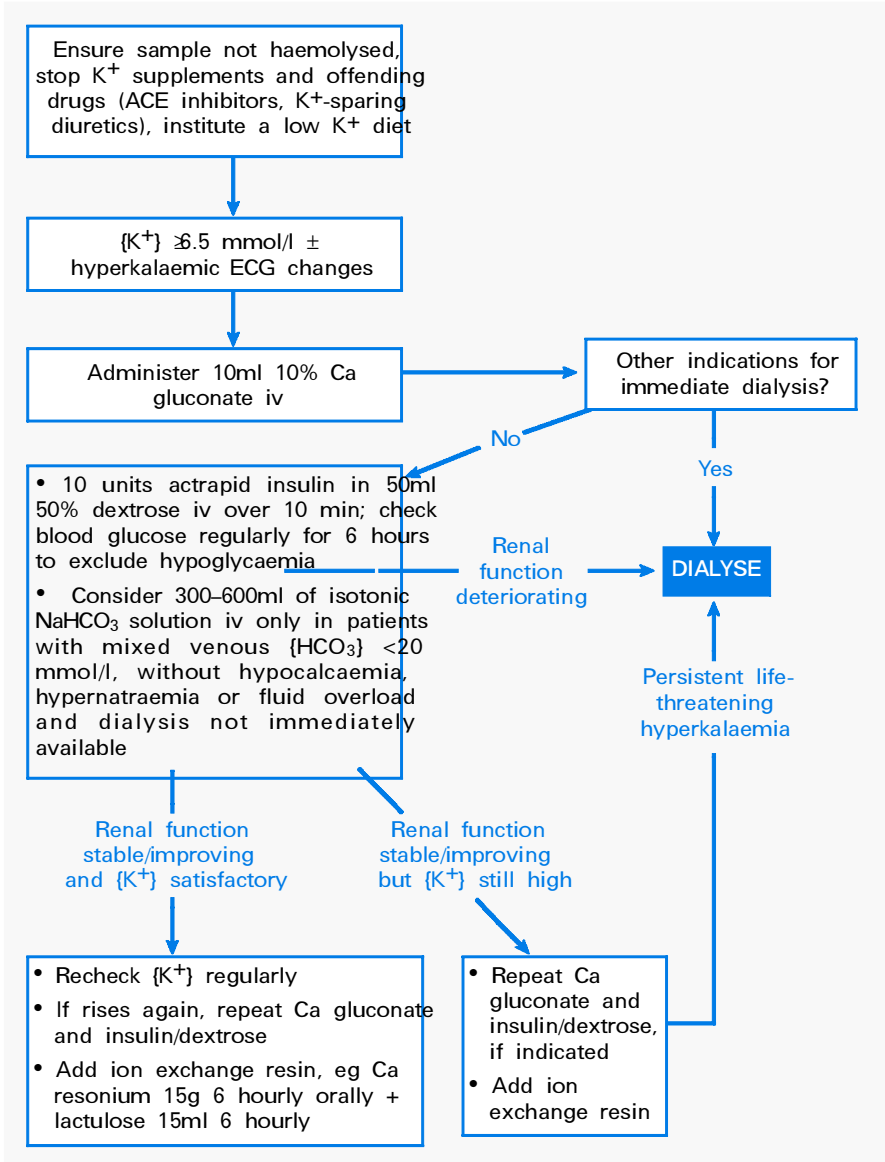
Making the patient safe

The two immediate aims of therapy in all cases are:

- rapid treatment of hyperkalaemia to avoid cardiac arrhythmias (Fig 2)
- avoidance of fluid overload.

Since significant salt and water retention does not occur until the GFR falls below 10–20 ml/min, pulmonary oedema typically occurs late in the course of ARF. Furthermore, many cases of ARF develop in the context of intravascular volume depletion rather

Fig 2. An algorithm for the management of hyperkalaemia in acute renal failure (ACE = angiotensin-converting enzyme; iv = intravenous) (adapted from Ref 1)



than fluid overload (eg hypovolaemia, sepsis, circulatory failure). However, fluid overload is readily precipitated by injudicious IV fluid infusion in the face of deteriorating renal function and oliguria. Fluid replacement should be stopped if there is clinical evidence of volume overload and patients should be referred for RRT. In the meantime, patients should be adequately oxygenated, and pulmonary oedema treated using vasodilators such as nitrates (to reduce venous return) and diuretics (to reduce intravascular volume). In refractory, life-threatening cases, venesection may be necessary in the intervening period before dialysis can be commenced. In hospitals without immediate access to haemodialysis facilities, patients may require transfer to the ICU for haemofiltration.

Renal replacement therapy

Urgent referral for dialysis is indicated in the presence of uncontrolled life-threatening metabolic sequelae, as follows:

- severe, refractory hyperkalaemia with risk of ventricular arrhythmia
- profound metabolic acidosis
- pulmonary oedema and fluid overload
- severe uraemia with uraemic encephalopathy, pericarditis or bleeding.

Patients with isolated ARF are likely to be haemodynamically stable and not particularly catabolic. Any form of RRT may be used, but in practice intermittent haemodialysis (IHD) is simple and effective. In haemodynamically unstable patients, IHD is relatively contraindicated, while the coexistence of ARF and cerebral oedema or ARF in the setting of hepatic failure precludes any form of intermittent therapy[16]. These patients are best managed with CRRT (eg continuous venovenous haemofiltration). The use of CRRT on the ICU has the advantage over IHD as it causes less haemodynamic instability, provides more efficient solute removal and allows correction of fluid overload, thereby facilitating administration of large obligatory fluid volumes to critically ill patients (eg drugs, nutrition). However, there is no evidence from clinical studies that CRRT improves patient survival compared with intermittent therapies, nor that it confers any advantage in terms of renal recovery, correction of acidosis and malnutrition, or improved outcome related to the use of biocompatible dialyses.

An equally efficient, but cheaper and less labour-intensive, alternative to CRRT may be slow, low-efficient daily dialysis (SLEDD) which has yielded promising results in preliminary studies[17].

General supportive measures

Drug therapy. Drug doses should be modified, with monitoring of drug levels where appropriate.

Infection. Patients with ARF are at major risk of sepsis as a result of relative immunosuppression (from malnutrition and uraemia) and instrumentation (indwelling dialysis catheters). Frequent inspection of vascular lines and regular line cultures are necessary, with rapid removal if evidence of infection is detected and early introduction of antimicrobial therapy.

Nutrition. Nutritional supplementation is important, particularly in patients with high protein catabolism who require a high calorie intake (35–50 kcal/kg body weight). However, excessive dietary protein enhances production of nitrogenous waste products and increases uraemia. Dietary modification in ARF aims to provide sufficient calories to avoid catabolism and starvation ketoacidosis, while minimising the production of nitrogenous waste. This is best achieved by restricting dietary protein intake to approximately 0.5–1 g/kg/day of protein of high biologic value (ie rich in essential amino acids) and by providing most calories in the form of carbohydrate (approximately 100 g/day). Enteral or parenteral nutrition, supplemented with vitamins, trace elements and glutamine, should be instituted in patients unable to achieve adequate oral intake. Dietary potassium intake should be restricted to 0.8 mmol/kg/day, especially in ARF patients not on dialysis.

Bleeding diathesis. Bleeding complications occur in ARF, leading to gastrointestinal haemorrhage (secondary to uraemic gastritis) and bleeding at sites of surgery and trauma. Prophylaxis against gastrointestinal bleeding is recommended with either H_2-antagonists or proton pump inhibitors. The aetiology of this bleeding tendency is multifactorial, and primarily related to a qualitative impairment in platelet function manifested by a prolonged bleeding time. In up to two-thirds of symptomatic patients, partial or complete correction of the bleeding tendency can be achieved by dialysis. Uraemic bleeding can be treated with 1-deamino-8-D-arginine vasopressin, an analogue of antidiuretic hormone which transiently releases endogenous stores of factor VIII-von Willebrand factor complexes from endothelial cells which increase platelet adhesion to the vessel wall[18]. The effect is maximal within one hour and lasts 4–8 hours, but is of limited use if bleeding is prolonged since tachyphylaxis rapidly occurs.

Cryoprecipitate is an alternative, efficient mode of correction, although the delayed onset of action (8–24 hours), obligate fluid volume and concerns about transmission of infection have limited its usefulness. Maintaining the haematocrit at 30% by blood transfusion may also reduce bleeding. Medications with antiplatelet activity such as aspirin should be discontinued.

When to refer to the nephrologist

It is recommended that advice from a nephrologist is sought for all cases of ARF, and early consultation can improve the outcome[5]. Transfer to the local renal unit will be necessary if patients with pre-renal ARF do not respond to appropriate treatment measures and if there are clear indications for RRT. If intrinsic renal disease is suspected, particularly RPGN, early referral is mandatory. Nephrologists should also be involved in

the management of patients at significant risk of developing ARF as a result of an elective intervention (eg the diabetic patient with pre-existing renal impairment who requires angiography).

Outcome

Patients with ATN have an oliguric renal failure phase usually lasting between one week and three months following acute injury, although recovery may occur later. The renal failure phase tends to be shorter if the primary insult (ischaemia, nephrotoxin) is rapidly corrected. Recovery is typically characterised by initial polyuria followed by restoration of normal urine volume. The polyuric phase results from improved glomerular filtration with delayed recovery of tubule function. Urinary concentration is impaired leading to the production of large quantities of dilute urine. Early recognition of the polyuric recovery phase of ATN is important to avoid volume depletion and recurrent renal injury. Treatment usually comprises IV fluid replacement with a combination of 0.9% saline and 5% dextrose in a 1:2 ratio, since the urinary sodium concentration may be up to 70 mmol/l. Potassium, calcium and magnesium replacement is often necessary and can be guided by measurement of urinary losses.

Death in patients with ATN is usually related to infection and the primary aetiology. In-hospital mortality from in-hospital ARF on the ICU remains high (~50%), and the development of ARF in addition to acute respiratory distress syndrome has a mortality rate of up to 80%. Importantly, recent evidence suggests that the development of ARF itself directly and independently contributes to mortality, highlighting both the importance of ARF prevention and the urgent requirement for novel therapeutic strategies in the management of these patients[5].

Future strategies

Several novel compounds have proved effective in the treatment of experimental ARF, but there has been little success in human clinical trials, for example, synthetic atrial natriuretic peptide[8] and recombinant human insulin-like growth factor-119. Trials of calcium channel antagonists, thyroxine and endothelin receptor antagonists have yielded similarly disappointing results.

Several exciting paths of investigation are ongoing, including studies in experimental ARF using hepatocyte growth factor, anti-intercellular adhesion molecule-1 antibodies, osteopontin, nitric oxide synthase inhibitors, platelet activating factor antagonists and α-melanocyte-stimulating hormone. As yet, there is no place for their use in humans outside clinical trials (for review, see Ref 15).

Conclusions

In-hospital ARF carries a high mortality rate, so attempts should be made to identify at-risk patients and prevent the development of ARF by suitable hydration and avoidance of nephrotoxins. ARF diagnoses that require specific treatment, particularly urinary tract obstruction and RPGN, must not be missed. The immediate priority for all patients with ARF is to make them safe from potentially life-threatening metabolic sequelae, with early referral to a nephrologist in case acute dialysis becomes necessary.

References

1 Glynne PA, Allen A, Pusey CD (eds). *Acute renal failure in practice*, 1st edn. London: Imperial College Press (2001, in press).

2 Firth JD. The clinical approach to the patient with acute renal failure. In: Winnearls C, Cameron JS, Ledingham D, Ritz E, Davison AM (eds). *Oxford textbook of nephrology*, 2nd edn. Oxford: Oxford University Press, 1997:1557–82.

3 Feest TG, Round A, Hamad S. Incidence of severe acute renal failure in adults: results of a community based study. *Br Med J* 1993;**306**:481–3.

4 Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 1983;**74**:243–8.

5 Star RA. Treatment of acute renal failure. Review. *Kidney Int* 1998;**54**:1817–31.

6 Klahr S, Miller SB. Acute oliguria. Review. *N Engl J Med* 1998;**338**:671–5.

7 Rahman SN, Conger JD. Glomerular and tubular factors in urine flow rates of acute renal failure patients. *Am J Kidney Dis* 1994;**23**:788–93.

8 Allgren RL, Marbury TC, Rahman SN, Weisberg LS, *et al*. Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. *N Engl J Med* 1997;**336**:828–34.

9 Solez K, Morel-Maroger L, Sraer JD. The morphology of 'acute tubular necrosis' in man: analysis of 57 renal biopsies and a comparison with the glycerol model. *Medicine (Baltimore)* 1979;**58**:362–76.

10 Brezis M, Rosen S, Silva P, Epstein FH. Renal ischemia: a new perspective. Review. *Kidney Int* 1984;**26**:375–83.

11 Thadhani R, Pascual M, Bonventre JV. Acute renal failure. Review. *N Engl J Med* 1996;**334**:1448–60.

12 Lieberthal W. Biology of acute renal failure: therapeutic implications. *Kidney Int* 1997;**52**(Suppl):1102–5.

13 Glynne PA, Picot J, Evans TJ. Co-expressed nitric oxide synthase and apical $1 integrins influence tubule cell adhesion following cytokine injury. *J Am Soc Nephrol* (in press).

14 Gaskin G. Management of rapidly progressive glomerulonephritis. *J R Coll Physicians Lond* 1997;**31**:15–8.

15 Lameire N, Vanholder R. Pathophysiologic features and prevention of human and experimental acute tubular necrosis. Review. *J Am Soc Nephrol* 2001;**12**(Suppl 17):S20–32.

16 Stevens PE. Renal replacement therapy in acute renal failure: choice of modality. In: Glynne PA, Allen A, Pusey CD (eds). *Acute renal failure in practice*, 1st edn. London: Imperial College Press (in press).

17 Vanholder R, Van Biesen W, Lameire N. What is the renal replacement method of first choice for intensive care patients? Review. *J Am Soc Nephrol* 2001;**12**(Suppl 17):S40–3.

18 Hilton R. Emergency consequences of acute renal failure: the uraemic syndrome. In: Glynne PA, Allen A, Pusey CD (eds). *Acute renal failure in practice*, 1st edn. London: Imperial College Press (in press).

19 Hirschberg R, Kopple J, Lipsett P, Benjamin E, *et al*. Multicenter clinical trial of recombinant human insulin-like growth factor I in patients with acute renal failure. *Kidney Int* 1999;**55**:2423–32.

Dr L Lightstone, Renal Section, Division of Medicine, Imperial College School of Medicine, Hammersmith Hospital, Du Cane Road, London W12 0NN.
Email: l.lightstone@ic.ac.uk