

Acute renal failure

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Abstract

The majority of cases of acute renal failure (ARF) occur in hospital, most commonly due to acute tubule necrosis caused by multiple nephrotoxic insults, particularly hypovolaemia, hypotension and nephrotoxic drugs. In-hospital ARF carries a high mortality rate, and every attempt should be made to identify at-risk patients and prevent its development by suitable hydration and avoidance of nephrotoxins. Out-of-hospital ARF typically presents as single organ disease, and, if the cause is readily identified and treated, often carries a good prognosis. ARF diagnoses that require specific treatment, particularly urinary tract obstruction and rapidly progressive glomerulonephritis, 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.

Keywords

Acute renal failure, acute tubule necrosis, glomerulonephritis, dialysis.

Introduction and definition

Acute renal failure (ARF) may be defined as an abrupt and sustained rise in plasma urea and creatinine, occurring over hours to days, due to a rapid decline in glomerular filtration rate (GFR).¹ This leads to loss of normal water and solute homeostasis, and potentially life-threatening sequelae including hyperkalaemia, acidaemia and ultimately fluid overload. The incidence of severe ARF (creatinine >500 mmol/l) is approximately 140 per million population per year.² Out-of-hospital ARF typically presents as single organ disease, and, if the cause is readily identified and treated, often carries a good prognosis. However, most cases of ARF occur in hospital, complicating around 5% of all medical and surgical admissions,³ and are usually associated with multiple nephrotoxic insults, particularly hypovolaemia, hypotension and nephrotoxic drugs. Despite the advent of renal replacement therapies (RRT), in-hospital mortality attributable to ARF remains high (up to 50%).⁴ This probably reflects the increasing number of critically ill patients undergoing continuous RRT on the intensive care unit (ICU).

Most cases of ARF present with oliguria. This defined as a reduction in urine output to less than 400 ml/day or approximately 0.5 ml/kg/h.⁵ In up to 20% of cases, however, 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.^{6,7} Conversion of oliguric ARF to a non-oliguric state is thus often considered to be a major objective of therapy, with prevention of ARF the primary goal wherever possible.

This review discusses the general approach to patients presenting with ARF, and highlights key management principles. A brief article of this nature can at best only hope to provide a general overview of such a vast subject, which is reviewed in greater detail elsewhere.^{8,9}

Aetiology of acute renal failure

ARF is most often caused by ischaemic (50%) or nephrotoxic (35%) renal injury, and frequently occurs as part of a multi-system disorder such as severe sepsis or trauma.⁴ Early recognition of potentially reversible causes of ARF allows rapid initiation of treatment, and may avoid the increased morbidity and mortality associated with established ARF. In clinical practice, ARF results from:

1. Reduced renal perfusion, e.g. hypovolaemia, reduced cardiac output - so-called **pre-renal ARF**.
2. **Intrinsic ARF**, caused by diseases affecting the tubulointerstitium, glomeruli or renal vasculature, e.g. following pre-renal ARF (post-ischaemic acute tubule necrosis), sepsis, nephrotoxic drugs, hepatorenal syndrome, immune-mediated nephritis.
3. Urinary tract obstruction - so-called **post-renal ARF**.

A comprehensive list of ARF aetiologies is given in Table 1, but a few causes deserve special mention:

Pre-renal ARF

Pre-renal ARF describes the reversible fall in GFR that occurs following renal hypoperfusion, typically due to hypotension and hypovolaemia. Under normal conditions intrarenal blood flow and

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GFR are tightly autoregulated over a mean arterial pressure (MAP) range of approximately 70-180 mm Hg. Therefore, in a patient without pre-existing hypertension, a MAP of >70 mm Hg is required to maintain normal renal function. When MAP falls to <70 mm Hg, autoregulation fails leading to vasoconstriction, with reduction in renal blood flow and GFR. Restoration of renal perfusion (e.g. by restoring intravascular volume) will reverse the decline in GFR; untreated, however, prolonged renal hypoperfusion leads to post-ischaemic acute tubule necrosis.

Acute tubule necrosis

Most in-hospital ARF is due to acute tubule necrosis (ATN). ATN is a histological diagnosis that describes the renal morphological changes common to several ARF aetiologies,¹⁰ particularly ischaemia, sepsis and nephrotoxic drugs such as angiotensin-converting enzyme inhibitors (ACEI) and non-steroidal anti-inflammatory drugs

(NSAIDs). ATN results either from prolonged hypoperfusion (post-ischaemic ARF), from direct tubule cell injury or a combination of both (see Table 1). A detailed description of the pathophysiology of ATN is beyond the scope of this article, and is reviewed elsewhere^{9,11,12}.

Acute tubulointerstitial nephritis

Acute drug-induced tubulointerstitial nephritis (TIN) is a common cause of ARF. The most frequently encountered precipitants 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 an important cause of ARF developing outside hospital, and should

Pre-renal ARF (55-60% of cases)		
Hypovolaemia	Haemorrhage Burns “3rd spacing” Gastrointestinal losses Renal losses	- pancreatitis, crush injury, intestinal obstruction - enteric fistulae/tube drainage, diarrhoea, vomiting - glycosuria, diuretics, post-obstructive diuresis
Hypotension	Cardiogenic shock Distributive shock	- sepsis, anaphylaxis
Renal hypoperfusion	Renal vasoconstriction Impaired autoregulation + MAP ~80 mm Hg Aortic aneurysm affecting renal vessels Renal artery thrombosis	- NSAIDs in elderly hypovolaemic patients, endotoxin - elderly patients, diabetes, atherosclerosis, bilateral renal artery stenosis + ACE inhibitor or All receptor antagonist
Oedematous states	Chronic heart failure Liver cirrhosis Hepatorenal syndrome	
Intrinsic ARF (35-40% of cases)		
Acute tubule necrosis	Ischaemia Direct tubule cell toxicity Disease of renal arteries Atheroemboli, cholesterol emboli Infarction Rapidly progressive glomerulonephritis	- following a “pre-renal” insult, sepsis - aminoglycosides, cisplatin, amphotericin B, radiocontrast, myoglobinuric ARF, sepsis, heavy metal poisoning Vasculitis
Disease of glomeruli/arterioles	Myeloma Thrombotic microangiopathy Malignant hypertension Scleroderma	- Goodpasture’s disease, Wegener’s granulomatosis, microscopic polyangiitis, systemic lupus erythematosus
Acute tubulointerstitial nephritis	Drug-related/allergic Parainfectious Paraneoplastic	
Post-renal ARF (<5% of cases)		
	Calculi Carcinoma Retroperitoneal disease Acutely neurogenic bladder Urethral stricture/stenosis blocked catheter	

Table 1. The aetiology of acute renal failure.¹

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Diagnosis	Clinical features/ aetiology	Important investigations	Treatment principles
Acute tubule necrosis	Hypotension Hypovolaemia Nephrotoxic drugs	Clinical diagnosis Urinary epithelial casts	Fluid resuscitation Treat primary aetiology Withdraw nephrotoxins
Rapidly progressive glomerulonephritis*	Fevers, arthralgia, rash, splinters, scleritis, neuropathy. Lung haemorrhage (GBM, WG, CSS, SLE, MEC, HSP) Asthma & nasal polyps (CSS) Epistaxis, granulomas, nasal collapse & deafness (WG)	Proteinuria Microscopic haematuria Urinary 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 therapy (e.g. corticosteroids, cyclophosphamide) Plasma exchange may be indicated (not for IE)
Acute Tubulointerstitial nephritis	Fever, rash and arthralgias ~2 weeks following drug exposure	Urinary white cell casts Eosinophiluria Eosinophilia	Withdraw offending agent Role for corticosteroids
Rhabdomyolysis	Crush injuries Alcohol Recreational drugs (e.g. ecstasy)	Brown urine Myoglobinuria False urine dipstick +ve for blood ↑ creatine kinase Severe hyperkalaemia Severe hyperphosphataemia	Hydration Alkaline diuresis Dialysis often required
Haemolytic uraemic syndrome	Diarrhoea +ve (E.coli O:H157) or Diarrhoea -ve (mitomycin, quinine, cyclosporin, malignant hypertension)	Microangiopathic haemolytic anaemia Thrombocytopaenia 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 use of prostacyclin**

*Causes of 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).

**Elinav E et al. Improvement in cholesterol emboli syndrome after iloprost therapy. BMJ 2002; 324:268-269

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ANCA - anti-neutrophil cytoplasmic antibody; C - Complement component; Ab - antibody.

Table 2. Acute renal failure: clinical features, investigations and treatment principles.²

always be considered even when features of systemic inflammation are not present (see Table 2). The diagnosis of RPGN must not be missed, since early treatment may prevent the development of end-stage renal failure.¹³

Myeloma

Myeloma is a relatively common cause of ARF presenting from the community, particularly in older patients. ARF can arise from hypercalcaemia, cast nephropathy, hyperuricaemia, hyperviscosity syndrome, light chain deposition or amyloid. Myeloma is associated with the presence of Bence-Jones proteinuria, a monoclonal band on serum ± urine protein electrophoresis and an immune paresis. These investigations should be performed routinely, particularly in elderly patients with renal failure, mild proteinuria and/or symptoms of hypercalcaemia.

Vascular causes of intrinsic ARF

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.

Urinary tract obstruction

Renal tract obstruction is an uncommon cause of ARF, accounting for fewer than 5% of cases. However, a rapid diagnosis of obstruction by clinical and ultrasound examination is imperative, as early intervention (e.g. bladder catheterisation or nephrostomy) relieves the obstruction, frequently corrects oliguria and significantly reduces the chance of developing intrinsic ARF.

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Prevention of acute renal failure

Given the high mortality associated with established in-hospital ARF, every effort should be made to identify those patients at greatest risk of ARF, thus allowing early institution of preventative therapies.

Identification of at-risk patients

The main risk factors are those causes of pre-renal ARF listed in Table 1, and the presence 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) is hyperbolic rather than linear (reviewed in¹). This means that a small rise in plasma creatinine, for example from 70 to 100 mmol/l, may indicate a marked fall in GFR and therefore significant renal impairment. Note that plasma creatinine is influenced by diet, and drugs that compete for tubule secretion of creatinine (e.g. trimethoprim, cimetidine, amiloride and 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:

$$\text{CrCl (ml/min)} = \frac{(140 - \text{age in years}) \text{ weight in kg}}{\text{serum creatinine } (\mu\text{mol/l})}$$

(correction for males x 1.23, females x 1.04)

Diabetic patients with microalbuminuria, hypertension or vascular disease, particularly those exposed to ACEI 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 (range 90–180 mm Hg), and may therefore suffer a fall in GFR at a MAP of 80–90 mm Hg rather than <70 mm Hg. This has important implications for the haemodynamic and fluid management of these patient subgroups, as outlined below.

Preventative therapy

Having identified at-risk patients, renal function and fluid balance should be closely monitored. The key preventative strategies include optimisation of renal perfusion, maintenance of an adequate diuresis and avoidance of nephrotoxic drugs. Renal perfusion is dependent on MAP and the effective circulating volume (ECV) of blood. ECV is related to the pressure as well as volume within the vasculature, and is normally regulated by baroreceptors, sympathetic nerves, the renin-angiotensin system and atrial natriuretic peptide. A reduction in ECV leads to a fall in renal perfusion and oliguria, as Na⁺ and water are reabsorbed. Restoration of ECV with fluid replacement is the single most important therapeutic maneuver that prevents progression from pre-renal to established ARF.

Clinical assessment of effective circulating volume

The clinical assessment of ECV depends on signs such as blood pressure, heart rate, jugular venous pressure (JVP)

and peripheral temperature, as well as the clinical context. Clinical signs consistent with reduced circulating volume include hypotension/postural hypotension, tachycardia, cool peripheries, reduced JVP and oliguria. Normally, ECV changes as extracellular fluid changes. This is typically seen in patients with haemorrhage following surgery or trauma, and evident by most of the clinical features above. Measurement of postural blood pressure is a sensitive method of detecting hypovolaemia, particularly in young patients who may have none of the associated signs of hypovolaemia.

Heart failure also affects ECV and hence renal perfusion. In acute heart failure following myocardial infarction, the reduction in cardiac output and therefore ECV is detected by baroreceptors, triggering Na⁺ and water absorption and therefore oliguria. Improving the cardiac output (e.g. with inotropes) improves renal perfusion and urine output. In sepsis, vasodilatation (characterised by warm peripheries, hypotension and a hyperdynamic circulation) leads to a reduction in ECV, although total volume of extracellular fluid remains the same.

Invasive monitoring

Where hypovolaemia is clinically apparent, the priority is to resuscitate the patient with fluid rather than delay treatment whilst establishing invasive monitoring. However, assessment of ECV is often difficult; not uncommonly, oliguria results from a combination of different aetiologies, e.g. the elderly patient with chronic heart failure, sepsis, dehydration and oliguria. In these cases, invasive monitoring may be helpful to assess ECV and guide fluid replacement. Methods of invasive monitoring include central venous pressure measurement (CVP), pulmonary artery occlusion pressure (PAOP) and oesophageal Doppler (in mechanically ventilated patients) monitoring.

CVP measurement is performed most commonly – a CVP <8 cm H₂O suggests reduced intravascular volume; a CVP 8–12 cm H₂O suggests normal or reduced intravascular volume; and a CVP elevated to >12 cm H₂O suggests increased intravascular volume. The CVP is also elevated in cardiac failure, tamponade, pulmonary hypertension, tricuspid regurgitation and hypovolaemia with excess sympathetic tone. A series of CVP measurements provides more information than one in isolation, particularly in response to intravenous fluid, provided they are consistent with other clinical measures of ECV. Monitoring of PAOP gives more information on left-sided cardiac filling pressures. Again, PAOP may not always be reliable, and does not directly measure ECV or give information on renal perfusion. In practice, the use of PA catheters is restricted to the ICU.

Clinical approach to fluid replacement in acute oliguria

Definite hypovolaemia with oliguria. In situations where hypovolaemia and oliguria are clinically apparent (haemorrhage, burns, ketoacidosis, pancreatitis), the priority is to restore ECV aiming to preserve renal

perfusion. In practice, blood or colloid is rapidly infused to maintain a MAP >70 mm Hg (or >80-90 mm Hg in patients with impaired renal autoregulation), with the rate of infusion directed by the clinical response. A continuous infusion of up to 2-3 l/h may be required initially.

Possible hypovolaemia with oliguria - Oliguria often occurs with few or no clinical signs of hypovolaemia. A fluid challenge is useful to help assess the ECV. Following a clinical assessment of ECV (pulse, postural blood pressure, JVP, peripheral temperature), 200 ml of colloid is given over 10 min. A rapid improvement in, for example, BP, tachycardia, or oliguria, would confirm hypovolaemia and prompt a further fluid challenge. If minimal or no change occurs, then the circulating volume may be optimal. In this situation CVP measurements may also be useful:

- CVP <5 cm H₂O with clinical features of hypovolaemia should be corrected with colloid until the CVP measures 8-12 cm H₂O.
- CVP 5-12 cm H₂O with clinical features of hypovolaemia, again should receive a fluid challenge. Often, as fluid is replaced, sympathetic vascular tone falls. This may be seen by the trend of CVP measurements over time and in response to fluid boluses. Following a fluid challenge, the CVP rises, only to fall with time as vascular tone falls. With this pattern, the aim is to continue fluid boluses until the CVP is maintained between 8-12 cm H₂O. Note that following a fluid challenge, a sustained rise in CVP of $\geq \sim 5$ cm H₂O suggests adequate ECV.
- CVP >12 cm H₂O, with clinical signs of fluid overload or cardiac failure. Intravenous fluid should be immediately stopped and the patient fluid restricted. In the situation of cardiac failure with oliguria, treatment of the underlying cause of cardiac failure is the priority. The use of inotropes to maintain cardiac output and renal perfusion should be considered.

Following fluid resuscitation and restoration of ECV, oliguria may be reversed and urine output increased. Re-evaluation of the patient, CVP and fluid balance will guide further fluid replacement. The aim should be to maintain the ECV and prevent further oliguria; generally, fluid input should equal urine output, with additional fluids administered to cover insensible losses (~500 ml/day). If MAP remains low (<70 mm Hg or <80-90 mm Hg in patients with impaired autoregulation) despite adequate fluid resuscitation, e.g. in cardiogenic or septic shock, transfer to a high dependency unit may be necessary for more invasive monitoring and inotropic support.

If oliguria persists despite achievement of an adequate MAP, then it is likely that the patient has developed established ATN. Diuretics are often used in this setting to promote a diuresis and to convert an oliguric state to a non-oliguric state, which may improve renal outcome.⁷ However, there is no evidence from human studies that loop diuretics (furosemide), osmotic diuretics (mannitol) or natriuretics (dopamine) prevent or alter the course of ARF.¹⁴⁻¹⁶ Interestingly, a recent study of patients with

chronic renal failure, suggested that the oral antioxidant acetylcysteine may prevent further deterioration in renal function following exposure to radiocontrast.¹⁷ Loop diuretics may allow less fluid restriction in oliguric ARF, 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, it is imperative that ECV is adequate, as diuresis in a hypovolaemic patient will further reduce renal perfusion and exacerbate renal injury. Furosemide may be administered as a bolus dose of 250 mg intravenously over 30 minutes. If oliguria persists following an initial bolus, then there is no advantage in giving further furosemide and the patient should be referred for dialysis.

Investigation and diagnosis of acute renal failure

The diverse aetiology of ARF often necessitates the use of a range of laboratory investigations to aid diagnosis and guide therapy; important examples are shown in Table 2. A standard clinical approach should be adopted for all patients presenting with ARF,⁸ and the following key issues addressed:

1. Establish whether ARF is acute, or due to acute-on chronic renal failure.

The medical history may indicate whether patients are likely to have pre-existing renal impairment, and it may be possible to obtain past creatinine measurements from old case notes. A normal haemoglobin level in patients presenting with renal failure, does not discriminate acute from chronic renal failure. There are several causes of anaemia in ARF, including thrombotic microangiopathy, haemorrhage and disseminated intravascular coagulation. Patients with chronic renal failure generally adapt to their biochemical and osmotic disturbances. Therefore, patients with markedly elevated plasma urea (>50 mmol/l) or creatinine (>1000 mmol/l) concentrations, who are not overtly symptomatic, are less likely to have ARF. Small renal size on ultrasound examination reflects chronic renal impairment, although renal size may be maintained in chronic diseases such as diabetes. ARF in the context of enlarged kidneys suggests a diagnosis of renal tract obstruction, amyloidosis, renal infiltration (e.g. lymphoma) or TIN. Patients may develop ARF on a background of chronic renal dysfunction, either due to exacerbation of an underlying renal disease (e.g. vasculitis), or due to unrelated renal insults (e.g. hypovolaemia, sepsis, nephrotoxins).

2. Exclude renal tract obstruction

Anuria suggests renal tract obstruction, although rarely can be secondary to renal cortical necrosis or necrotising GN. 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 in all cases by ultrasonography. Occasionally, obstructive ARF occurs in the absence of a non-dilated

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upper renal tract, particularly in the presence of renal tract malignancy. In these cases, serial ultrasound scans, CT scanning or nuclear scintigraphy may reveal the underlying obstruction.

3. Ensure adequate ECV

The clinical assessment of ECV has been discussed. Renal hypoperfusion often results in a disproportionate increase in the plasma urea:creatinine ratio, as urea is reabsorbed passively along with sodium and water (unlike creatinine, which is not re-absorbable). However, a raised urea:creatinine ratio may also be produced by a high protein diet, increased catabolism (e.g. post-surgery, infection), gastrointestinal bleeding, corticosteroid therapy and tetracyclines. Alternatively, it can result from a reduction in the plasma creatinine concentration due to reduced body muscle mass. The urea:creatinine ratio must therefore be interpreted with caution. Myoglobinuric ARF, secondary to rhabdomyolysis, is associated with a low urea:creatinine ratio because muscle injury releases creatinine resulting in 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 (e.g. pregnancy).

Plasma and urine biochemistry can help to distinguish pre-renal: Acute renal failure from ATN. The physiological response to volume depletion (pre-renal ARF) of tubule salt and water reabsorption, results in appropriate oliguria, high specific gravity on urine dipstick testing, low urinary Na^+ concentration (usually <20 mmol/l), low fractional excretion of Na^+ (FENa, equal to sodium clearance/creatinine clearance, $<1\%$) and high urine osmolality (>500 mOsm/kg). In ATN, this mechanism is disrupted, primarily due to medullary ischaemia, with loss of tubule responsiveness to anti-diuretic hormone. Urinary Na^+ concentration is usually >40 mmol/l and FENa $>2\%$, with osmolality similar to that of plasma (<350 mOsm/kg). In the absence of hypovolaemia, low urinary Na^+ concentrations may also be seen with haemoglobinuria, vasculitis and in patients with the hepatorenal syndrome or cardiac failure. A very low urinary Na^+ (<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, i.e. optimisation of ECV and avoidance of fluid overload. During the diuretic recovery phase of ARF, measurement of urinary electrolytes provides a useful guide to 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 may be completely anuric. Renal vascular Doppler studies or angiography will confirm the diagnosis.

5. Determine whether parenchymal renal disease other than ATN 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 multi-system disease, and physical examination can be informative (e.g. 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 inflammatory renal disease. Haematuria, dysmorphic red blood cells $\pm$ 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 auto-immune disease/vasculitis and will usually require 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 have occurred, 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. This may be sufficient, in cases of pre-renal ARF or non-oliguric ATN, to reverse renal failure and, in the case of oliguric ATN, obviate the need for RRT. If established ARF develops, therapy is directed at (1) making the patient safe, instituting rapid treatment of life-threatening metabolic disturbances, (2) initiating RRT when appropriate, (3) general supportive measures, and (4) therapeutic interventions targeted at the primary aetiology (see Table 2).

(1) Making the patient safe

In all cases, the immediate aims of therapy are rapid treatment of (i) hyperkalaemia to avoid cardiac arrhythmias and (ii) avoidance and treatment of fluid overload.

(i) Hyperkalaemia

All cases of ARF complicated by potentially life-threatening hyperkalaemia (ECG changes, plasma $[\text{K}^+]$ ≥ 6.5 mEq/l) warrant early referral to a nephrologist as dialysis is likely to become necessary, despite the interim treatment measures described below. All ARF patients should be prescribed a low-potassium diet. Treatment for hyperkalaemia can be subdivided as follows (adapted from⁹):

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- *Antagonising the Cardiac Effects of Hyperkalaemia* - indicated when ECG changes are present or plasma $[K^+]$ ≥ 6.5 mEq/L. Cardiac myocytes are stabilised by the intravenous administration of 10 mL of 10% calcium gluconate infused over 2 – 3 min into a large vein, and can be repeated after 5 min if ECG changes persist. Important features of this treatment include onset of action 1 – 3 min, duration of action 30 – 60 min, no effect on extracellular $[K^+]$ or K^+ excretion and it may exacerbate digoxin toxicity.

- *Promoting Intracellular K^+ Transfer:*

Insulin and dextrose infusion - is the mainstay of treatments promoting cellular K^+ uptake. By upregulating Na^+/H^+ exchange across cell membranes, insulin increases intracellular $[Na^+]$ and promotes cellular $[K^+]$ uptake by the $3Na^+/2K^+$ -ATPase. To prevent hypoglycaemia, approximately 2 g of glucose are administered with each unit of soluble insulin, and a standard cocktail is 50 ml 50% dextrose with 15 units soluble insulin, given intravenously over 10 min. Because of the risk of delayed hypoglycaemia, regular monitoring of blood glucose is essential for 6 h after treatment, and is particularly important when treatment is given prior to transfer to a renal unit. Treatment is best avoided in patients about to dialyse, since intracellular movement of K^+ may reduce its clearance via the extracorporeal circuit. Important features of this treatment include onset of action 15 – 45 min, duration of action 4 – 6 h, expected decrease in plasma $[K^+]$ 0.6–1.5 mEq/L and delayed hypoglycaemia reported in up to 75% of patients.

Sodium bicarbonate infusion - By neutralising extracellular H^+ in acidotic and hyperkalaemic patients, intravenous $NaHCO_3$ may promote Na^+/H^+ exchange across cell membranes, thereby increasing intracellular $[Na^+]$ and upregulating the $3Na^+/2K^+$ exchanger. If $NaHCO_3$ solution is administered to those with mixed venous $[HCO_3^-]$ < 20 mEq/L, who are neither hypocalcaemic nor hypernatraemic. It should not be relied upon as monotherapy. 300 – 600 mL of 1.26% $NaHCO_3$ solution are given intravenously over 15 – 30 min. In the setting of hyperkalaemic cardiac arrest, give 50 mL 8.4% $NaHCO_3$ and repeat as necessary (monitor arterial pH). Important features of $NaHCO_3$ treatment for hyperkalaemia include onset of action 5–15 min, duration of action 60–120 min. Dangers of treatment include salt/water overload, overshoot alkalosis, reduction in plasma free $[Ca^{2+}]$ causing tetany, precipitation of Ca salts if co-administered with calcium gluconate. Note that the treatment for worsening acidosis in established ARF is dialysis, and not bicarbonate therapy.

- *Removing K^+ from the Body:*

Cation exchange resins - Calcium and sodium polystyrene sulphonate (Calcium resonium and Resonium A) are ion exchange resins which exchange cations (predominantly K^+) for calcium and sodium

respectively. The exchanged K^+ ions are subsequently excreted with the stool. Administration is either oral, in a dose of 15 g three to four times daily, or rectally as a suspension of 30 g resin in 100 mL 2% medium viscosity methylcellulose and 100 mL water (retained for 9 h). Always co-prescribe osmotic laxatives, e.g. lactulose 10–20 mL 8 hourly. Approximately 1 mEq of K^+ is excreted for each gram of resin administered. Important features of this treatment include onset of action 30–60 min rectally / 2–4 h orally, duration of action 4–6 h. Dangers of treatment include constipation, hypercalcaemia (Ca Resonium), salt / water overload (Resonium A) and hypomagnesaemia. Dialysis - In the absence of functioning kidneys, haemodialysis (HD) is the most efficient means of removing body K^+ , and can clear 35 mmol K^+ /h using a dialysate $[K^+]$ of 1–2 mmol/L. Peritoneal dialysis removes K^+ at approximately 20% of this rate. Certain forms of ARF are associated with severe, early, and often refractory hyperkalaemia, notably rhabdomyolysis, tumour lysis and massive haemolysis; rapid institution of acute HD is usually required.

(ii) Fluid overload

Since significant salt and water retention does not occur until the GFR decreases to 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 than fluid overload (e.g. hypovolaemia, sepsis, circulatory failure). However, fluid overload is readily precipitated by injudicious intravenous 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 interim, 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.

(2) Renal replacement therapy

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

- Severe hyperkalaemia with risk of ventricular arrhythmias (e.g. plasma $[K^+]$ ≥ 6.5 mEq/L)
- Severe metabolic acidosis (e.g. pH < 7.15 , base deficit > 10)
- Pulmonary oedema and fluid overload
- Severe uraemia with uraemic encephalopathy, pericarditis or bleeding

Patients with isolated ARF are more likely to be haemodynamically stable. Any form of RRT may be used, but in practice intermittent HD is simple and effective. Until recently, there has been no consensus on the

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appropriate HD dose in patients with ARF. However, a recent prospective study concluded that daily haemodialysis was associated with better control of uraemic symptoms, earlier resolution of renal failure and longer survival than was a conventional alternate day regimen.¹⁸ In haemodynamically unstable patients, intermittent HD is relatively contraindicated, and the coexistence of ARF and cerebral oedema, or ARF in the setting of hepatic failure, precludes any form of intermittent therapy.¹⁹ These patients are best managed with continuous RRT (CRRT; e.g. 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 (e.g. drugs, nutrition). However, to date, there are no data from clinical studies that demonstrate CRRT improves patient survival compared to intermittent therapies, nor that CRRT confers any advantage with regards to renal recovery, correction of acidosis and malnutrition, or that outcomes are improved related to the use of biocompatible dialysers.²⁰

(3) 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 detected, and early introduction of antimicrobial therapy. Once oligoanuria is established, urinary catheters should be removed as they become a source for sepsis.
- Nutrition – nutritional supplementation is important, particularly in those 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 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 (i.e. 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 the ARF patient not on dialysis.

- Bleeding diathesis – bleeding complications include gastrointestinal haemorrhage (secondary to uraemic gastritis) and bleeding at sites of surgery and trauma. We recommend prophylaxis against gastrointestinal bleeding with either H₂ 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 (dDAVP), an analogue of antidiuretic hormone which transiently releases endogenous stores of Factor VIII: von Willebrand Factor complexes (FVIII:vWF) from endothelial cells which increase platelet adhesion to the vessel wall.²¹ The effect is maximal within 1 hour and lasts 4–8 hours, but is of limited use if bleeding is prolonged, since tachyphylaxis rapidly occurs. Maintaining the haematocrit at 30%, by blood transfusion, may also reduce bleeding. Medications with antiplatelet activity, such as aspirin, should be discontinued.

Outcome

Patients with ATN have an oliguric renal failure phase that usually lasts between 1 week and 3 months following acute injury, although this tends to be shorter if the primary insult 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 and ion depletion and recurrent renal injury. Treatment usually comprises intravenous fluid replacement with a combination of 0.9% saline and 5% dextrose in a 1:2 ratio, since the urinary Na⁺ 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 very high (~50%), and the development of ARF in addition to the acute respiratory distress syndrome results in mortality rates 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.⁴

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