

3

Acute renal failure

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Acute renal failure (ARF) is defined as the rapid cessation of renal excretory function within a time frame of hours or days, accompanied by a rise in serum urea and creatinine, and accumulation of nitrogenous waste products in a patient whose renal function was previously normal. It is usually, but not always, accompanied by a fall in urine output. The condition is potentially reversible, and in routine clinical practice, measurement of serum creatinine is used to follow the changes in glomerular filtration rate (GFR).

Definition

There are various working definitions of ARF, including:

- an increase in serum creatinine of $>50 \mu\text{mol/L}$
- an increase in serum creatinine of $>50\%$ from baseline
- a reduction in calculated creatinine clearance of $>50\%$
- the need for dialysis.

Confusingly, the patient may be anuric ($<50 \text{ mL urine/24 hours}$), oliguric ($<400 \text{ mL urine/24 hours}$), pass normal volumes of urine or may even be polyuric. The urine produced may be of poor quality, however, with very few waste products. The diagnosis of ARF is made on plasma biochemistry, with an elevated serum creatinine, urea and possibly potassium. Oliguria is usually indicative of failure of both glomerular and tubular function. In contrast to chronic renal failure, there is no early loss of endocrine function.

Caution is required when interpreting measurements of serum creatinine in ARF for several reasons:

- Creatinine production depends on muscle mass, and though normally constant for an individual, it can increase in patients with acute muscle injury.
- Because of the reciprocal relationship between creatinine concentration and GFR, small changes in GFR close to the normal range have much less effect on serum creatinine than small changes when GFR is already significantly reduced.
- Changes in serum creatinine concentration lag behind changes in GFR. The serum creatinine may continue to increase for several days after a marked reduction in the GFR, even if the GFR has subsequently started to improve.

Incidence

The incidence of ARF is difficult to state precisely because it depends on the parameters by which it is defined. The incidence of severe ARF (serum creatinine $>500 \mu\text{mol/L}$) in the general population is estimated to be approximately 70–140 per million of the population,¹ and around half of these will require dialysis. Less severe ARF (serum creatinine $\leq 177 \mu\text{mol/L}$ or an increase of 50% above baseline) occurs in about 210/million/year. One hospital survey revealed some degree of renal impairment in around 5% of all admissions.² In intensive care units (ICU), however, the figure is much higher, with at least 15% of admissions having renal

impairment, of which the cause is sepsis in approximately 50% of cases. The financial implications of renal impairment are considerable: the cost of a survivor who had renal failure leaving ICU is 70 times that of a patient without renal impairment.²

Clinical features

Since ARF involves the acute retention of nitrogenous waste products, salt, water, potassium and acid, the physical signs and symptoms encountered include:

- nausea and vomiting
- peripheral oedema
- breathlessness
- pulmonary oedema
- itching
- pleural effusion
- weakness
- pericarditis
- depression of consciousness
- oliguria
- convulsions.

An episode of ARF usually lasts between 7 and 21 days providing the primary insult is corrected in a reasonable time.

Irreversible ARF usually occurs either in patients with pre-existing renal disease or in those who experience repeated ischaemic or nephrotoxic insults.

The mortality rate for ARF is variable. Patients with non-oliguric ARF have a relatively low mortality (10–40%), possibly because they have less severe underlying disease or perhaps because they have been treated more promptly or aggressively. A particularly high mortality rate (80–90%) is found in older patients and in those with serious complications such as pre-existing cardiovascular or respiratory disease, severe burns, hepatorenal syndrome, sepsis and multi-organ failure.

Causes

Conventionally, the causes of ARF are classified by renal anatomy into pre-renal, renal and post-renal causes. This approach is somewhat oversimplified, since many cases of ARF have a mixture of pre, post and renal components. Take, for example, a traumatic injury causing rhabdomyolysis and ARF. The injury and associated muscle swelling causes a fall in effective arteriolar blood volume (EABV) and hence pre-renal impairment. The myoglobin released from the muscle causes renal vasoconstriction (also pre-renal), tubular injury (renal) and tubular obstruction (post renal).³ Nevertheless, since there is no alternative classification in clinical use and it is a useful way of considering the kidney, the causes of ARF will be described under these headings.

Pre-renal failure

Pre-renal ARF is caused by inadequate perfusion of essentially normal kidneys, in which the EABV is reduced. It is a normal physiological response to hypotension or hypovolaemia, resulting in intense renal conservation of sodium and water at the expense of a decreased GFR. Renal function usually returns to normal rapidly once the underlying cause is corrected.

The kidneys are adept at regulating their blood supply over a variety of perfusion pressures, and such autoregulation is highly effective in healthy individuals. This means that quite severe perturbations of blood pressure or interference with the usual adaptive responses of the kidney are required to cause renal dysfunction in the normal kidney. The operative word here is normal, since in disease states, for example hypertension, this autoregulation may be disordered or reset, leading to renal dysfunction at blood pressures that would ordinarily be quite adequate to maintain renal perfusion.

Table 3.1 lists some of the causes of ARF.

The traditional signs of sodium and water depletion include tachycardia, hypotension, postural hypotension, reduced skin turgor, reduced ocular tension (sunken eyes), collapsed

Table 3.1 Some of the causes of acute renal failure

Hypovolaemia	Trauma, burns, surgery, pancreatitis, haemorrhage, gastrointestinal losses, exudative dermatitis, liver failure, nephrotic syndrome, hepatorenal syndrome
Loss of peripheral resistance in which the vascular bed is dilated thereby reducing the circulating volume	Sepsis, endotoxaemia, shock, general anaesthesia, overuse of antihypertensives, anaphylactic shock, surgery
Decreased cardiac output	Cardiogenic shock, heart failure, pulmonary embolism, myocardial infarction, cardiac arrhythmias, post-cardiac surgery
Renovascular obstruction	Atherosclerosis, thrombosis, embolism, dissecting aneurysm
Altered renal autoregulation	NSAIDs, ACE inhibitors, ciclosporin, tacrolimus

peripheral veins and cold extremities. One of the physiological responses is a reduction in renal perfusion, which in turn may lead to intrinsic renal damage with a consequent acute deterioration in renal function. This state may be caused by a significant haemorrhage, or by septicaemia, in which the vascular bed is dilated thereby reducing the effective circulating volume. It may also be caused by excessive sodium and water loss from the skin, urinary tract or gastrointestinal tract. Excessive loss through the skin by sweating occurs in hot climates and is rare in the UK, but it also occurs after extensive burns. Gastrointestinal losses are associated with vomiting or diarrhoea. Urinary tract losses often result from excessive diuretic therapy but may also occur with the osmotic diuresis caused by hyperglycaemia and glycosuria in a diabetic patient.

Infection causes a large proportion of ARF by causing the systemic inflammatory response syndrome (SIRS). SIRS can be precipitated by a variety of organisms (including bacteria, viruses and fungi) and can lead to multi-organ failure which has a mortality in excess of 60%.⁴ The mediators of multi-organ failure include haemodynamic changes (principally systemic hypotension and altered tissue bed perfusion), complement activation and cytokine release.

Acute tubular necrosis

Acute tubular necrosis (ATN) comes from the insults that cause pre-renal ARF, but in circumstances lasting long enough to cause ischaemic

injury to renal tubules. This leads to a prolonged reduction in GFR that sometimes persists for weeks after correction of the initiating insult. However, the condition is potentially recoverable, provided the initial insult to the kidneys is removed, and renal perfusion is maintained.

Intrinsic renal failure

Intrinsic renal failure is caused by any factor that causes damage either to the kidney itself or the surrounding vasculature. Table 3.2 lists the numerous mechanisms that can lead to intrinsic ARF.

Renal causes of ARF can be subdivided into four categories; vascular, glomerular, tubular and interstitial.

Vascular

Blockage of renal blood vessels caused by atheroembolic disease or foreign material leading to an inflammatory reaction which obliterates the lumen (e.g. cholesterol emboli) can cause ARF. Occasionally, endothelial damage causes intimal proliferation and luminal obliteration (e.g. in scleroderma renal crisis or accelerated phase hypertension).

The vasculitides cause inflammation and necrosis in the vessel wall upstream of, or in, the glomerular tuft (after all the glomerulus is merely a modified blood vessel). The size of the vessel involved determines the symptoms and

Table 3.2 Mechanisms that can lead to intrinsic acute renal failure

Acute tubular necrosis	General surgery Cardiac surgery Vascular surgery (e.g. repair of abdominal aortic aneurysm, involving cross-clamping of the aorta) Obstetric complications Sepsis Acute heart failure Burns
Nephrotoxicity	Including aminoglycosides and amphotericin
Intravascular coagulation	Including hypertension, pre-eclampsia, eclampsia, haemolytic–uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), scleroderma, disseminated intravascular coagulation (DIC), sepsis
Acute tubular necrosis	Post-ischaemia Nephrotoxins (drugs, contrast media, organic solvents, herbal medicines, snake venom, mushrooms, heavy metals) Myoglobinaemia Hypercalcaemia
Contrast nephropathy	A specific form of nephrotoxicity characterised by renal vasoconstriction and avid sodium retention
Impaired renal perfusion + drug-induced impairment of autoregulation	ACE inhibitors, NSAIDs, plus atherosclerotic renal vascular disease or hypovolaemia
Hepatorenal syndrome	Reversible intense renal vasoconstriction and sodium retention complicating cirrhosis
Poisoning	Including paracetamol, often after recovery from liver damage
Rhabdomyolysis	Following crush injury, drug overdose, status epilepticus
Atheroembolism (cholesterol embolism)	Spontaneous or a complication of angiography, angioplasty or thrombolysis
Raised intra-abdominal pressure (abdominal compartment syndrome)	Caused by intra-abdominal pressure >25 mmHg (e.g. post-operative abdominal exploration, tense ascites)
Renal embolism	Endocarditis, cardiac thrombus
Infiltration	Including leukaemias, lymphoma, multiple myeloma
Urate nephropathy	Complication of chemotherapy for acute leukaemia or lymphoma
Myeloma	Cast nephropathy, light-chain deposition disease, amyloidosis, sepsis and hypercalcaemia can all cause renal damage
Hypercalcaemia	Sarcoidosis, myeloma
Intravenous immunoglobulin	Probably results from osmotic damage to proximal tubular cells caused by sucrose in some IV immunoglobulin preparations
Renal parenchymal disease	Rapidly progressive glomerulonephritis (systemic vasculitis, Goodpasture's syndrome, systemic lupus erythematosus, Wegener's granulomatosis) Acute interstitial nephritis Haemolytic uraemic syndrome Cryoglobulinaemia

Table 3.2 continued

Renal parenchymal disease (continued)	Acute allergic tubulo-interstitial nephritis (penicillins, NSAIDs, recreational drugs) Bacterial endocarditis Infections (Legionnaires' disease) Granulomas (tuberculosis) Crystals (hyperuricaemia, hypercalcaemia)
Malignant hypertension	Untreated primary ('essential') hypertension or a complication of chronic glomerulonephritis, or scleroderma renal crisis
Renal vein thrombosis	Complication of malignancy or pre-existing nephritic syndrome
Acute pyelonephritis	Seldom causes acute renal failure, although may be more likely to do so in the elderly and in those taking NSAIDs Infection in patients with diabetes and partial obstruction (e.g. from papillary necrosis) may cause pyelonephritis and acute renal failure

signs and also provides a way of classifying these diseases.

Microangiopathic haemolytic processes are processes in which endothelial damage is the prime mover, leading to activation of coagulation, red cell destruction, tubular obliteration and downstream necrosis. The classical examples include pre-eclampsia and the haemolytic uraemic syndrome.

Glomerular

The glomeruli may be affected by various usually immune-mediated insults classified by their histological appearance (the glomerulonephritides). These can present either as the nephrotic syndrome (proteinuria >3 g/24 hours, oedema, hypoalbuminaemia) with or without renal dysfunction, or as a nephritic illness with nephritic features and/or hypertension and haematuria, often accompanied by renal dysfunction. Drugs are sometimes responsible for inducing glomerular disease.

Tubular

Tubular function may be compromised by numerous insults. Tubular cells have adapted to exist in an ischaemic environment normally, but any insult which reduces further the already critical supply of metabolites can cause renal dysfunction by causing acute tubular necrosis. Tubular damage usually results in a reduction in

urine output, although the reasons for this have not been completely elucidated. Certainly when tubular cells are damaged they slough off the tubular basement membrane into the tubular lumen causing some degree of tubular obstruction. In addition, glomerular filtrate is not constrained within the tubular lumen and leaks back into the capillaries without change in composition. Finally, and probably most importantly, renal blood flow is reduced in ATN and blood is diverted towards the medulla away from the cortex, bypassing the glomeruli. Renal vasoconstriction is caused by, among other things, tubuloglomerular feedback from increased sodium chloride delivery to the macula densa, sympathetic stimulation, angiotensin II, endothelin and thromboxanes.

Metabolic derangements may also lead to renal dysfunction, the most common cause of which is probably hypercalcaemia, which can cause ARF. Another metabolic problem that can lead to ARF is hypothyroidism.

Interstitial

The interstitium is that part of the kidney that is not vascular, glomerular or tubular. As the kidney relies on its tightly coordinated structure to function, any disruption to this highly interdependent architecture can result in renal failure. An interstitial infiltration with inflammatory cells including eosinophils is a characteristic of many drug-associated cases of ARF.

Acute bacterial pyelonephritis can lead to infiltration with inflammatory cells and interstitial scarring and some viral infections are associated with marked interstitial oedema that can cause ARF. Autoimmune diseases (e.g. systemic lupus erythematosus or mixed connective tissue diseases) cause an interstitial infiltrate that may be irreversible. Very occasionally, the kidney is infiltrated with cells from lymphoma or leukaemia causing interstitial expansion and ARF. One unusual cause of renal failure is that of the compressed or 'Page kidney'. In this situation compression of the renal parenchyma by a haematoma (e.g. following a renal biopsy or trauma) can cause acute renal dysfunction.⁵

Analgesic nephropathy is a special form of renal disease in which there is often renal papillary necrosis and a history of analgesic administration. It is now much less common in the UK where many of the strongly associated drugs have been withdrawn (e.g. phenacetin).⁶

Drug-induced acute renal disease

Drug-induced renal failure is well recognised, but the frequency with which it occurs with particular drugs is unknown. It is, however, important to be aware of the types of drug that can induce renal failure because there may be a specific antidote or, if suspected and acted on early, the failure may be reversible.

Despite a large blood supply, the kidneys are always in a state of incipient hypoxia because of their high metabolic activity, and any condition that causes the kidney to be underperfused may be associated with an acute deterioration in renal function. However, such a deterioration may also be produced by nephrotoxic agents, including drugs.

- **Non-steroidal anti-inflammatory drugs (NSAIDs)** in particular are associated with renal damage, and even a short course of an NSAID (such as diclofenac) has been associated with ARF, especially in older patients. The main cause of NSAID-induced renal damage is inhibition of prostaglandin synthesis in the kidney, particularly prostaglandins E₂, D₂ and I₂ (prostacyclin). These prostaglandins are all potent vasodilators and

consequently produce an increase in blood flow to the glomerulus and the medulla. The maintenance of blood pressure in a variety of clinical conditions, such as volume depletion, biventricular cardiac failure or hepatic cirrhosis with ascites, may rely on the release of vasoconstrictor substances such as angiotensin II. In these states, inhibition of prostaglandin synthesis may cause unopposed renal arteriolar vasoconstriction, which again leads to renal hypoperfusion. NSAIDs impair the ability of the renovasculature to adapt to a fall in perfusion pressure or to an increase in vasoconstrictor balance.

- **Angiotensin-converting enzyme (ACE) inhibitors** may also produce a reduction in renal function by preventing the angiotensin II-mediated vasoconstriction of the efferent glomerular arteriole, which contributes to the high-pressure gradient across the glomerulus. This problem is important only in patients with renal vascular disease, particularly those with bilateral renal artery stenoses, causing renal perfusion to fall. In order to maintain the pressure gradient across the glomerulus, the efferent arteriolar resistance must rise. This is predominantly accomplished by angiotensin-induced efferent vasoconstriction, as is shown in Figure 3.1. If ACE inhibitors are administered, this system is rendered inoperable and there is no longer any way of maintaining an effective filtration pressure. This leads to a fall in GRF and the development of ARF.
- **Contrast media**, especially the ionic variety (iodinated) used for radiological scans, are also known nephrotoxins, especially in patients with already compromised renal function. There are thought to be two mechanisms of action behind this toxicity. The contrast media cause vasospasm which in turn leads to tubular ischaemia and reduced oxygen tension. In addition, oxidative stress causes an increased formation of free radicals within the tubules, leading to further damage.
- **Iatrogenic factors**, including fluid and electrolyte imbalance and drug nephrotoxicity, can be identified in over 50% of cases of ARF and also play a large role in many cases

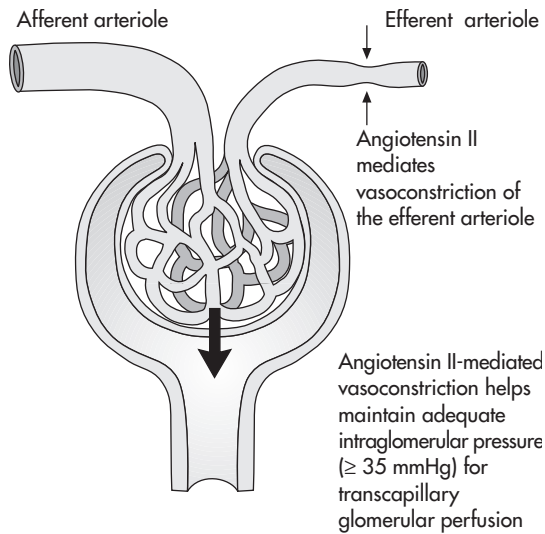


Figure 3.1 The role of angiotensin II in maintaining adequate intraglomerular pressure.

of community-acquired ARF. Other causes of drug-induced renal failure are discussed in Chapter 11. It has been estimated that up to 20% of individuals over the age of 65 are prescribed diuretics, with a lesser number receiving an NSAID; consequently, there is a large population of elderly patients susceptible to renal damage in the event of any insult to the kidney. ARF that requires dialysis is fortunately rare, with only 50–70 patients per million of the population affected annually, but less severe degrees of impairment may occur in up to 5% of hospital inpatients.

Post-renal failure (obstruction)

Post-renal failure or obstructive nephropathy involves obstruction of urinary outflow, leading to increased pressure within the renal collecting systems and resulting in reduced GFR, reduced tubular reabsorption of sodium and water, and acquired renal tubular acidosis, phosphaturia and other abnormalities of tubular function. These abnormalities may persist even after relief of the cause of the obstruction. Table 3.3 lists the most common causes of obstructive nephropathy.

Table 3.3 Common causes of obstructive nephropathy

Bladder outflow	Benign prostatic hypertrophy or prostatic carcinoma Infiltrative bladder cancer causing bilateral vesico-ureteric obstruction Neurogenic bladder
Ureteric obstruction	Bilateral stone disease Crystal deposition (urate, sulfonamides, aciclovir, cisplatin) Pelvic tumours Papillary necrosis Retroperitoneal fibrosis (with or without abdominal aortic aneurysm) Radiation fibrosis Urethral strictures

Symptoms/signs

The initial cause of the ARF is important in determining the symptoms and signs of the presentation. There may be none until late on, when signs of fluid overload, oedema and hypertension and hyperkalemia might be presenting features.

Hyperkalaemia may cause cardiac arrest without warning. Not all patients have the same susceptibility to the cardiac effects of hyperkalaemia, but the risk of cardiac arrest can be judged by electrocardiogram (ECG). Pulmonary oedema is the most serious complication of salt and water overload in ARF, often arising from inappropriate administration of intravenous fluids to oliguric patients. In severe cases, patients are restless and confused, with sweating, cyanosis, tachypnoea, tachycardia and widespread wheeze or crepitations in the chest. Further investigation will show arterial hypoxaemia and widespread interstitial shadowing on chest X-ray.

Distinguishing acute from chronic renal impairment

One question that must be asked is whether the renal failure is really acute. Raised serum creatinine in an acutely unwell patient can be caused by acute (ARF), acute-on-chronic, or chronic (CRF) renal failure. These presentations have different prognoses and may require fundamentally different management. Points to help distinguish between them include:

- Comparing any previous measurements of serum creatinine with the patient's current biochemistry. Pre-existing chronic renal impairment can be excluded if a relatively recent previous measurement of renal function was normal.
- A history of several months' vague ill-health, nocturia or pruritus, and findings of skin pigmentation, anaemia, long-standing hypertension or neuropathy suggest a more chronic disease.
- Renal ultrasonography to determine size and echogenicity of the kidneys. It is noteworthy that renal size is normal in most patients with ARF.
- Anaemia is a major feature of CRF, but it may occur early in the course of many diseases that cause ARF.
- Bone disease – evidence of long-standing renal bone disease (e.g. radiological evidence of hyperparathyroidism, greatly elevated parathyroid hormone (PTH) levels) is diagnostic of CRF, but hypocalcaemia and hyperphosphataemia may occur in both ARF and CRF.

Management

Regardless of the cause, the same general treatment principles apply to all patients who develop ARF. These include removing nephrotoxic insults (e.g. drugs): in some instances the nephrotoxins may need to be removed by dialysis or adsorption (e.g. after aspirin overdose) or specific antidotes may be needed in addition to dialysis (e.g. N-acetylcysteine in paracetamol overdose). In the case of obstructive ARF, the

cause of the obstruction should be removed if possible.

Fluids

In pre-renal failure, urine output and renal function should improve when intravascular volume is restored, thus improving renal perfusion. The fluid infused should be blood, colloid or sodium chloride, and should mimic the nature of the fluid lost as closely as possible. Aggressive, early fluid resuscitation is the intervention most likely to have a positive effect on the course of pre-renal ARF and ARF caused by ATN. It must be guided by regular clinical assessment of the patient's circulating volume, aided by measurements of central venous pressure (CVP) or even pulmonary capillary wedge pressure.

Sodium chloride 0.9% is an appropriate choice of intravenous fluid, as it replaces both water and sodium ions in a concentration approximately equal to plasma. Conversely, should water depletion with hypernatraemia occur, isotonic solutions that are either free of, or low in, sodium are available (e.g. dextrose 5% or sodium chloride 0.18% with dextrose 4%). Patients should be observed continuously and the infusion stopped ideally when features of volume depletion have been resolved but before volume overload has been induced.

Fluid balance

Strict fluid balance charts are often ordered in patients with ARF. It is useful to know the fluid input and output, but these charts are notoriously inaccurate. Over-reliance on them also carries the danger that fluid replacement will be adjusted according to the recent output rather than the clinical state of the patient. Positive fluid balance is a necessary part of the resuscitation process for patients with effective or true hypovolaemia.

However, in extremely overloaded patients, it may be necessary to restrict fluid intake to the urine volume passed in the previous 24 hours + other losses, for example, insensible losses of 500 mL/day. This fluid allowance may be

increased if the patient exhibits signs of hyperventilation, sweating, fever, wound or drain losses.

Possibly the most common cause of ARF is the peripheral vasodilation that occurs in septic shock. In such cases it would be appropriate to infuse a colloid as well as sodium chloride as this would help to restore the circulating volume. It is important to remember, however, that not all shocked patients are hypovolaemic and some, notably those in cardiogenic shock, could be adversely affected by a fluid challenge.

Urine output

Another reason for measuring urine output is to assess renal function. Anuria and severe oliguria are diagnostic of severe ARF, but otherwise urine volume is of little help. For example, a GFR of 100 mL/min (6000 mL/h) normally gives a urine flow rate of about 60 mL/h because of reabsorption of 99% of the filtrate delivered to the renal tubules. However, a GFR of 1 mL/min combined with complete failure of tubular reabsorption (resulting from tubular damage, as in ATN, or from high doses of drugs that inhibit tubular reabsorption (e.g. dopamine, furosemide) would also give a urine output of 60 mL/h. Changes in urine flow are therefore a very poor guide to changes in GFR, and must be interpreted along with all other available clinical information. Urethral catheters are often placed to enable accurate measurement of urine flow rate. However, they are the single most important source of hospital-acquired Gram-negative sepsis, so should not be placed without good reason, and should be removed as soon as possible.

Fluid challenges

These are often given in the hope that they will stimulate diuresis. It is both illogical and dangerous to give further fluid to a patient who has already been fully resuscitated. If the patient remains oliguric, the extra fluid load may cause life-threatening pulmonary oedema. The only rational use of a 500 mL fluid bolus is when given in combination with CVP measurements;

administration of a fluid bolus to a hypovolaemic patient causes only a transient increase in CVP, whereas a more sustained rise is seen in patients approaching euvolaemia.

Dopamine, loop diuretics and mannitol

In ATN, volume repletion does not restore renal function, and urine output usually remains low (<30 mL/h). There is no evidence that any treatment improves renal function or accelerates renal recovery. Dopamine has been used at low doses (~2 ng/kg per min) for many years as a reno-protective agent, in the belief that it causes vasodilatation of the renal vascular bed, restores renal blood flow and thereby improves GFR. While its use has been controversial, a multi-centre randomised double-blinded placebo-controlled trial has shown no benefit to using low-dose dopamine infusion in patients with renal dysfunction with the systemic inflammatory response syndrome.⁷ The weight of evidence has swung firmly against the use of low-dose dopamine and its routine use in incipient or established ARF should be discontinued.

The use of a loop diuretic infusion in patients with non-oliguric ARF has been popular. The theory is that the most metabolically active cells in the nephron are the first to suffer tubular necrosis in renal underperfusion. Loop diuretics reduce the activity of the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ pump, which is highly metabolically active, thus releasing some metabolic energy towards essential subcellular pathways favouring survival in a critical incipient tubular cell death. They are also purported to flush out tubular casts. Many units give a trial of furosemide (e.g. 500 mg IV over 8 hours, or 1 g over 24 hours, if a small dose has produced no effect). Treatment is then continued according to response, although if the urine output in a euvolaemic patient does not respond to a large dose of furosemide, further therapy should be discontinued in order to prevent further damage to the tubules.⁸

Mannitol has been used to promote an osmotic diuresis and has been advocated by some in cases of incipient ARF and contrast media-induced nephrotoxicity. However it has not been shown to offer any reno-protective effects in any field of ARF and may cause

significant renal impairment itself by causing an osmotic nephrosis and increase tubular workload by increasing solute delivery.⁹

Loop diuretics and dopamine can both increase urine output by reducing tubular reabsorption of filtrate, which give the false impression that GFR has improved. The ability to mount a diuresis in response to either drug is probably an indication that the patient may have a better prognosis overall. Unless the patient is significantly volume overloaded, the diuresis caused by these drugs can exacerbate ATN by causing further hypovolaemia. Administration of diuretics to patients with a low CVP or to those at risk of hypovolaemia is similarly clinically unjustified.

Choice of resuscitation fluid

Adequate intravascular volume replacement is essential in the management of ARF. However, controversy continues over the optimal fluid for correction of hypovolaemia.

Crystalloids

Crystalloids (e.g. 0.9% sodium chloride, 5% glucose, Hartmann's solution) are cheap and safe, but rapidly distribute between the vascular space and the extracellular space, resulting in oedema, pleural effusions and ascites if used in large volumes, particularly in the presence of increased endothelial permeability (as in systemic inflammatory response syndrome). In cases where the patient has symptomatic metabolic acidosis, 1.26% sodium bicarbonate solution may be infused instead of 0.9% sodium chloride. The two solutions are both isotonic with blood, but the bicarbonate will help correct the acidosis.

Colloids

Colloids (e.g. human albumin, dextrans, hydroxyethyl starch (HES), modified gelatins) are used in the hope that they will remain in the vascular space for longer and hence restore microcirculatory flow more efficiently. This theory holds true for cases of simple hypo-

volaemia. However, when plasma protein levels may be increased as a result of haemoconcentration, crystalloids will probably be more effective. In sicker patients with sepsis, endothelial permeability to macromolecules is often increased, with the danger that these molecules will leave the circulation, elevate interstitial oncotic pressure and exacerbate the accumulation of fluid in the extracellular space.

In the UK, the available colloid solutions include gelatin preparations, dextran solutions and HES solutions. None of the available preparations are free of potentially serious side-effects. In particular, dextrans can cause anaphylactoid reactions and HES solutions may disrupt coagulation mechanisms and cause renal impairment. In a trial comparing gelatin with HES 200/0.62 in critically ill patients there was twice the incidence of ARF in the HES-treated group. However, more recent trials comparing gelatin solution with the low-molecular-weight, low-substitution HES 130/0.4 solution have shown a vastly improved safety profile with regard to renal function and coagulation with the new HES.^{10,11}

A Cochrane meta-analysis comparing synthetic colloids with crystalloids concluded that there was no proven clinical benefit for the use of colloids in resuscitation. However, they continue to be widely used in clinical practice on the basis of their theoretical advantages.

Renal replacement therapy

Many patients with mild-to-moderate ARF can be managed on general medical or surgical wards, but those with multiple organ failure should be managed on an ICU. Patients with ARF requiring renal replacement therapy (RRT) (i.e. those with rapidly increasing serum creatinine, oliguria, especially those with impending or established pulmonary oedema, hyperkalaemia and severe metabolic acidosis) should be managed on either a renal ward or an ICU.

There is currently little evidence to guide decisions on when to instigate RRT in ARF. The options for RRT are usually continuous arterio-venous or veno-venous haemofiltration (CAVH/CVVH), continuous arterio-venous or veno-

venous haemodiafiltration (CAVHDF/CVVHDF) and intermittent haemodialysis.

Additional points

There are several other practical points to be considered in the management of patients with ARF, some of which are especially relevant to pharmacists. These include:

- Amendment of drug doses: prescriptions should be closely scrutinised and, where necessary, the doses of drugs must be altered so that they are appropriate for the patient's level of renal function. Since the level of renal function may be in a state of flux in someone with ARF, it is important to continue to monitor renal function and re-adjust doses as necessary.
- In order to allow the already damaged kidneys to recover, it is also vital to avoid any further nephrotoxic insults wherever possible, for example, the use of NSAIDs and aminoglycosides. If they must be used, ensure that the dose is appropriate, and minimise the length of treatment. Try to use an alternative, non-nephrotoxic agent wherever possible.
- Maintain adequate nutritional therapy: a good rough guide is a protein intake of 0.6 g/kg per day, increasing to 1 g/kg if the patient being dialysed. Calorie intake should be 50–100% above the patient's resting energy expenditure (25 kcal/kg per day). Consult a specialist renal dietician where possible.
- Monitor the patient's biochemical parameters closely, including daily weight, fluid balance, U + Es (especially potassium, calcium and phosphate), a full blood count, and liver function tests. Treat any serious anomalies appropriately.
- Treat hyperkalaemia if the serum potassium is >6 mmol/L (see also Chapter 2). Severe hyperkalaemia with changes in the ECG should be treated as an emergency. Dialysis will correct hyperkalaemia, but it may not be possible to initiate this measure immediately.

A salbutamol nebuliser will lower serum potassium levels transiently by stimulating uptake into cells. Intravenous calcium (10% calcium gluconate, 10 mL over 60 seconds) is given to 'stabilise' the cardiac membranes, but does not alter the serum potassium level. Rapidly acting insulin 10 units (with 50% glucose, 50 mL) given IV over 5–10 minutes, stimulates the Na⁺/K⁺-ATPase in muscle and liver, driving potassium into cells and reducing the serum concentration by 1–2 mmol/L over 30–60 minutes. This does, however, render the potassium 'unavailable' to a dialysis procedure and should therefore be avoided if imminent dialysis is contemplated. Cation exchange resins (e.g. calcium polystyrene sulfonate (Calcium Resonium) 15 g) orally or rectally 6-hourly may be given to absorb potassium into the gut lumen. They require 4 hours to take effect, and lead to severe constipation if taken without laxatives, but may be a useful 'stopgap' measure.

- Patients with ARF are very prone to developing stress ulceration, so a proton pump inhibitor, H₂ blocker or sucralfate should be prescribed as per local protocol.

Outcome

Acute renal failure is a life-threatening condition. In a series of more than 1000 patients requiring dialysis, mortality was 40%.¹² Outcome depends directly on pathogenesis. If due to obstruction which is successfully relieved, or ATN where haemodynamic parameters return to normal quickly, then recovery approaches 100%. However if due to glomerulonephritis, prognosis depends on severity of damage and may be irrecoverable if too many glomeruli are involved. In such cases, the patient will need to remain on dialysis permanently.

Conclusion

Acute renal failure is common in hospitalised patients and is most often due to ATN. It is

associated with a significant mortality and morbidity and is expensive to treat. Drugs play an important role in the pathogenesis of ARF. The pharmacist can play an important role in identifying possible pathogens, ensuring that

the patient does not receive any further nephrotoxic compounds during the recovery phase, and advising on appropriate dose adjustments for drugs given to the patient while undergoing RRT.



CASE STUDY

Mr VC is a 65-year-old man (68 kg, 175 cm) who presents to casualty with nausea, vomiting and profound diarrhoea. Two weeks ago he presented to his GP with a painful right metatarsal pharyngeal joint (due to gout), for which his GP prescribed colchicine 500 µg 4-hourly for 2 days. Unfortunately, the patient became violently sick after four doses and discontinued this medication and went back to the GP who then prescribed:

- Indometacin 50 mg three times a day
- Ranitidine 150 mg twice daily.

The gout pain is now resolving.

On admission, Mr VC was pale, lethargic and breathless.

Past medical history:

- Hypertension 1 year
- Type 2 diabetes 5 years.

Medication:

- Bendroflumethiazide 5 mg every morning (for the last six months – increased from 2.5 mg)
- Ramipril 2.5 mg every morning (started six months ago)
- Gliclazide 40 mg twice daily.

Biochemistry:

- Sodium 137 mmol/L (135–150 mmol/L)
- Potassium 6.9 mmol/L (3.5–5.2 mmol/L)
- Urea 28.5 mmol/L (3.2–6.6 mmol/L)
- Creatinine 386 µmol/L (60–110 µmol/L)
- Bicarbonate 18 mmol/L (22–31 mmol/L)
- Phosphate 1.7 mmol/L (0.9–1.5 mmol/L)
- Corrected calcium 2.6 mmol/L (2.2–2.5 mmol/L)
- pH 7.26 (7.36–7.44)
- Glucose 10.8 mmol/L
- 24-hour urine output 600 mL.

Mr VC is admitted to hospital under the diabetic team.

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**CASE STUDIES** (continued)

Q1. What patient and pharmaceutical factors may have precipitated acute renal failure in this patient?

Q2. What are the main pharmaceutical problems and how might they be managed?

Mr VC is treated for his hyperkalaemia, put on a sliding scale insulin infusion, and rehydrated with 4 L of sodium chloride 0.9%, until he has a central venous pressure (CVP) of 12.

After 2 days, his serum creatinine has fallen to 168 $\mu\text{mol/L}$. However, a further 2 days later, it is noted that he is again failing to pass urine, although he appears to have a palpable bladder, and his serum creatinine has again risen to 272 $\mu\text{mol/L}$. This suggests urinary retention, so the decision is made to insert a urinary catheter.

Following insertion of the catheter, Mr. VC passed 2 L of urine in the next 24 hours, but then spiked a temperature of 38.5°C and became hypotensive. A diagnosis of urinary sepsis was made, and because it was the weekend, and with no other laboratory data available, the new senior house officer (SHO) prescribed gentamicin 475 mg IV daily.

Q3. Comment on the appropriateness of the prescribed antibiotic therapy. What advice would you provide regarding this?

Mr VC is given the gentamicin dose of 475 mg IV on the Sunday. On Monday morning, the pharmacist notes that both the drug and the dose are inappropriate for Mr VC, given his degree of renal impairment. The drug is discontinued on the drug chart, but a gentamicin level is taken anyway, and is reported back as 8.6 mg/L, so it is calculated it will take Mr VC several more days to clear that one dose. The prescription is changed to co-amoxiclav IV 600 mg three times a day.

His serum creatinine is monitored, and over the course of the next few days, the serial levels are 272, 284, 290, 237, 188, 135 $\mu\text{mol/L}$. He is switched to oral co-amoxiclav, and his renal function continues to fall.

Mr VC is discharged from hospital on day 10, with a serum creatinine of 112 $\mu\text{mol/L}$.

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