

RENAL DISEASE

(1) ACUTE RENAL FAILURE

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The first in a series of four articles on renal disease discusses the causes and treatment of acute renal failure

Acute renal failure (ARF) is defined as the cessation of renal excretory function within a period of hours or days, accompanied by a rise in serum urea and creatinine. It is usually, but not always, accompanied by a fall in urine output. This may present as anuria (a complete lack of urine output) or oliguria (low urine output, ie, less than 15 to 20 ml/hour, or about 500ml/day, in a normal adult) and 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.

INCIDENCE

The incidence of ARF in the general population is estimated to be approximately 70 to 140 cases per million.¹ Around half of these will require dialysis. Some degree of renal

impairment is found in around 5 per cent of all hospital admissions.² However, in intensive care units (ICUs) the figure is much higher, with over 15 per cent of patients admitted to hospital having renal impairment. In about half of these cases, the cause is sepsis. The financial implications of renal impairment are considerable. The cost of one survivor leaving ICU with renal failure is 70 times that of a patient without renal impairment.³

CAUSES

Conventionally, the causes of ARF are classified by renal anatomy into pre-renal, renal and post-renal. However, this is an oversimplification, since many cases have a mixture of pre-, post- and renal components. 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 in this article. Pre- and post-renal causes will be discussed first, and then renal causes.

Healthy kidneys are adept at regulating their blood supply over a variety of perfu-

sion pressures. This means that quite severe disturbance of blood pressure, or interference with the kidney's usual adaptive responses, are required to cause renal dysfunction in the healthy kidney. The operative word here is normal, since in disease states such as hypertension, autoregulation may be defective or reset, leading to renal dysfunction at blood pressures that would ordinarily be adequate to maintain renal perfusion.

Pre-renal Pre-renal causes of ARF are those in which the effective arteriolar blood volume (EABV) is reduced and the kidneys are deprived of blood flow. Haemorrhage, excessive gastrointestinal loss, sepsis, heart failure and liver failure are the most common culprits. In addition, some drugs can cause volume depletion, for example, diuretics, laxatives or any substances that induce diarrhoea or vomiting (see Panel 1).

Infection often causes ARF by inducing the systemic inflammatory response syndrome (SIRS). SIRS can be precipitated by bacteria, viruses and fungi, and can lead to multiorgan failure that has a mortality in ex-

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cess of 60 per cent.⁴ The mediators of multi-organ failure include haemodynamic changes (principally systemic hypotension and altered tissue bed perfusion), complement activation and cytokine release.

So far, we have considered only gross haemodynamic disturbances that reduce EABV. We must now specifically consider disease of the renal vascular bed. This may be, for example, an atheromatous plaque partially occluding the renal artery or widespread atheromatous accumulation in the terminal branches of the renal vascular tree. This rarely causes ARF in itself; more often renal dysfunction is insidious, and presents as hypertension and chronic renal failure.

Elderly patients are particularly prone to ARF caused by a combination of pre-existing renal vascular disease and taking an angiotensin converting enzyme (ACE) inhibitor. This is occurs when there is any significant degree of renal artery stenosis, because renal perfusion pressure falls. To maintain the pressure gradient across the glomerulus (the driving force behind formation of glomerular filtrate), efferent arteriolar resistance must rise. This is predominantly accomplished by angiotensin-induced efferent vasoconstriction. If ACE inhibitors are administered, this system is rendered inoperative and there is no longer any way of maintaining effective filtration pressure. This leads to a fall in glomerular filtration rate (GFR) and acute renal failure.

Dissection of the aorta or vasculitis of the large or medium-sized blood vessels (eg, Takayasu's arteritis), although rare, should be considered as pre-renal conditions. Vasculitis involving small blood vessels (eg, microscopic polyangiitis or Wegener's granulomatosis) is much more common, but is probably best considered under renal causes of ARF.

Certain drugs acting on the systemic or renal vasculature can cause a reduction in systemic blood pressure and hence in renal perfusion pressure (eg, overtreatment with antihypertensive drugs). Vasopressors, such as noradrenaline and angiotensin, can also cause renal vasoconstriction when used in the ICU.

Other examples of drugs causing ARF with a pre-renal component are non-steroidal anti-inflammatory drugs (NSAIDs), which impair the ability of the renal vasculature to adapt to a fall in perfusion pressure or to an increase in vasoconstrictor balance. They do this by preventing the production of prostacyclin and prostaglandin E₂, both of which are potent renal vasodilators that are vital for maintaining the renal microcirculation.

Post-renal Any blockage to urinary outflow will cause some degree of post-renal dysfunction. Post-renal dysfunction can be subdivided according to the site at which the blockage occurs (see panel above).

The most common cause is bladder outflow obstruction arising from prostatic hypertrophy. For completeness, renal vein thrombosis should also be considered as a cause of ARF.

Causes of post-renal dysfunction

URETER/BLADDER

Benign prostatic hypertrophy or prostate carcinoma
Cervical cancer and other pelvic masses
Bladder masses (tumours or clots)
Neurogenic bladder
Urethral stricture
Retroperitoneal mass/fibrosis

INTRARENAL

Intratubular obstruction — crystals (eg, indinavir)
Paraproteins (eg, myeloma)
Stones or calculi (eg, calcium phosphate)

PELVIC

Transitional cell carcinoma
Pelvic malignancy leading to extrinsic compression of the ureters
Inflammatory aortic aneurysm

Renal Renal causes of acute renal failure can be subdivided into four categories:

- Vascular
- Glomerular
- Tubular
- Interstitial

Vascular The lumen of blood vessels may become blocked. This can be caused by atheroembolic disease or by foreign material (see Panel 2) causing an inflammatory reaction that obliterates the lumen (eg, cholesterol emboli). Occasionally, endothelial damage causes intimal proliferation and luminal obliteration (eg, in scleroderma renal crisis or accelerated-phase hypertension).

The various types of vasculitis cause inflammation and necrosis in the vessel wall upstream of, or in, the glomerular tuft. The size of the vessel involved determines the symptoms and signs and also provides a way of classifying vasculitis.

Microangiopathic haemolytic processes are those in which endothelial damage causes activation of coagulation, red cell destruction, tubular obliteration and downstream necrosis. Classical examples include pre-eclampsia and the haemolytic uraemic syndrome.

Glomerular The glomerulus can be affected by various, usually immune-mediated, insults that are classified by their histological appearance.

These can present either as nephrotic syndrome (proteinuria greater than 3g/24h, oedema and hypoalbuminaemia) with or without renal dysfunction, or as illness with nephrotic features and/or hypertension and haematuria, often accompanied by renal dysfunction. Drugs are sometimes responsible for inducing glomerular disease (see Panel 3).

Tubular Tubular cells have adapted to exist in an ischaemic environment normally, but any insult that reduces their supply of metabolites can cause acute tubular necrosis and renal dysfunction (see Panel 4). Tubular damage usually results in a reduction in urine output, although the reasons for this are not known.

When tubular cells are damaged, they slough off the basement membrane into the tubular lumen causing a degree of tubular obstruction. In addition, glomerular filtrate leaks back into the capillaries without change in composition. Most importantly, renal blood flow is reduced and blood is diverted away from the cortex towards the medulla, bypassing the glomeruli. The causes of renal vasoconstriction include tubuloglomerular feedback from increased sodium chloride delivery to the macula densa, sympathetic stimulation, angiotensin II, endothelin and thromboxanes.

Interstitial The interstitium is the part of the kidney that is not vascular, glomerular or tubular. As the kidney relies on its highly coordinated structure to function, any disruption can result in renal failure. Interstitial infiltration with inflammatory cells, including eosinophils, is a characteristic of many drug-associated cases of acute renal failure (see Panel 5).

Acute bacterial pyelonephritis can lead to infiltration of the interstitium with inflammatory cells and interstitial scarring. Some viral infections are associated with marked interstitial oedema that can cause ARF. Autoimmune diseases, such as systemic lupus erythematosus or mixed connective tissue diseases, cause an interstitial infiltrate that can be irreversible. Occasionally, the kidney is infiltrated with cells from lymphoma or leukaemia, causing interstitial expansion and ARF.

One unusual cause of renal failure is compressed kidney, in which compression of the renal parenchyma by a haematoma (eg, following a renal biopsy or trauma) can cause acute renal dysfunction.⁸

DRUG-INDUCED ACUTE RENAL FAILURE

Drug-induced renal failure is well recognised, but the frequency with which it is

PANEL 1: DRUGS THAT CAUSE PRE-RENAL DISEASE

Drugs that compromise the circulation and hence decrease renal perfusion will have an indirect adverse effect on renal function. Volume depletion resulting from aggressive diuretic therapy or from major gastrointestinal losses caused by drug-induced diarrhoea and/or vomiting can compromise renal function.

Antihypertensives Laxatives
Diuretics NSAIDs
Vasoconstrictors

PANEL 2: DRUGS THAT CAUSE CRYSTALLURIA

Uric acid crystals can form as a result of probenecid therapy or following cancer chemotherapy. In both situations there is an increase in uric acid excretion, for which allopurinol prophylaxis should be used. Some drugs can form crystals within the renal tract, although this is rarely a clinical problem if the patient is sufficiently hydrated.⁵

Acetazolamide	Nitrofurantoin
Foscarnet	Pentamidine
Indinavir	Sulphonamides
Mercaptopurine	Triamterene
Methotrexate	Vitamin C

caused by particular drugs is unknown. It is important to be aware of the types of drug that can induce renal failure because there may be a specific antidote and early treatment could reverse the failure.

Renal dysfunction after exposure to a causative drug can occur within a few hours but can be delayed for weeks or months. Recovery of renal function usually occurs over one month to a year following drug withdrawal, but permanent impairment can result.

Papillary necrosis is a radiological diagnosis in which the normal cupped shape of the renal papillae is replaced by a clubbed appearance. This indicates that the collecting system architecture has been destroyed. Papillary necrosis can complicate interstitial nephritis, analgesic nephropathy or other systemic conditions, such as diabetes mellitus and sickle cell disease.

Analgesic nephropathy is a 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 United Kingdom, where many of the drugs with which it is strongly associated have been withdrawn, eg, phenacetin.⁹

Analgesic combinations, especially those containing salicylates, caffeine or paracetamol, seem to increase the risk of developing chronic tubular interstitial disease and papillary necrosis. Analgesic nephropathy is still underdiagnosed, because patients often under-report their use of analgesics.⁶

SYMPTOMS AND SIGNS

The cause of ARF tends to determine the symptoms and signs of the presentation. There may be no symptoms or signs until an advanced stage, when fluid overload, oedema, hypertension and hyperkalaemia might be presenting features. Hyperkalaemia can 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. It often arises from inappropriate ad-

ministration 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 shows arterial hypoxaemia, and widespread interstitial shadowing is visible on the chest X-ray.

One question that must be asked is whether the renal failure is acute or chronic. Pre-existing chronic renal impairment can be excluded if a relatively recent measurement of renal function is normal. A history of several months of vague ill health, nocturia or pruritus, together with skin pigmentation, anaemia, long-standing hypertension or neuropathy, suggests chronic disease.

Metabolic derangements may cause renal dysfunction, the most common cause being hypercalcaemia, which can cause ARF. Other metabolic problems that can lead to ARF include hypothyroidism.

TREATMENT

Regardless of the cause, the same general treatment principles apply to all patients who develop ARF. These include removing nephrotoxic insults by dialysis or adsorption, if necessary. Specific antidotes may be needed in addition to dialysis (eg, N-acetylcysteine for paracetamol overdose.)

In pre-renal failure, urine output and renal function should improve when intravascular volume is restored, thus improving renal perfusion. The fluid infused should mimic the nature of the fluid lost as closely as possible and should, therefore, be blood, colloid or saline. Patients should be observed continuously and the infusion stopped when features of volume depletion have been resolved, but before volume overload has been induced.

In acute tubular necrosis, if volume replacement does not restore renal function and urine output remains low (less than 30ml/h), there is no evidence that any treatment improves renal function or accelerates renal recovery. Dopamine has been used at low doses (about 2ng/kg/min) for many years as a renoprotective agent. However, a recent trial has shown no benefit in using low-dose dopamine infusion in patients with renal dysfunction and SIRS.¹⁰ The weight of evidence is now swinging firmly against the use of low-dose dopamine and its routine

use in incipient or established ARF should stop.

Recently, 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 sodium-potassium-chloride (Na⁺/K⁺/Cl⁻)-pump, which is highly metabolically active. This releases some metabolic energy for use by essential subcellular pathways, which helps to prevent incipient tubular cell death. Many renal units give trial doses of intravenous furosemide (eg, 2 to 10mg/h) if a small dose has produced no effect. Treatment is then continued according to response.

Mannitol has been used to promote osmotic diuresis, and has been advocated by some for incipient ARF and for contrast medium-induced nephrotoxicity. However, this drug has no renoprotective effects and can cause significant renal impairment by triggering osmotic nephrosis. It may also increase tubular workload by increasing solute delivery.¹¹

Severe hyperkalaemia, with changes to the ECG, should be treated as an emergency. Dialysis will correct hyperkalaemia, but it might not be possible to start dialysis immediately. A salbutamol nebuliser will lower serum potassium levels transiently by stimulating uptake into cells. Intravenous calcium (10 per cent calcium gluconate, 10ml given over 60 seconds) is given to stabilise cardiac membranes but it does not alter serum potassium levels. Rapidly acting insulin (10 units given IV over 5–10 minutes with 50ml of 50 per cent glucose) stimulates Na⁺/K⁺-ATPase in muscle and liver, driving potassium into cells and reducing the serum potassium concentration by 1–2 mmol/L over 30–60 minutes. However, this renders the potassium unavailable and this technique should, therefore, be avoided if imminent dialysis is contemplated.

Cation exchange resins (eg, calcium polystyrene sulphonate 15g given orally or rectally 6-hourly) can be given to adsorb potassium. The potassium is then kept within the gut lumen and excreted by defaecation. These resins require four hours to take effect, and cause severe constipation if taken without laxatives. However, they can be a useful stopgap.

PANEL 3: DRUGS THAT CAUSE GLOMERULONEPHRITIS

Acute glomerulonephritis is an immune-mediated disease where antigen-antibody complexes accumulate in the glomerulus and precipitate an inflammatory response. The GFR is reduced, with salt and water retention, expansion of the intravascular volume and hypertension. The source of the antigen is not discovered in all cases, although infection is a major cause of the disease, and several drugs are known to act as allergens.⁶

Allopurinol	Levamisole	Probenecid
Chlorpropamide	NSAIDs	Psoralen
Dapsone	Penicillamine	Quinidine
Gold	Penicillin	Rifampicin
Halothane	Phenindione	Thiazides
Hydralazine	Procainamide	Tolbutamide

PANEL 4: TUBULOTOXIC DRUGS

As well as being caused by decreased renal perfusion, tubular necrosis can be caused by a direct toxic effect of a drug. It can occur with normal doses, but more often results from high-dose treatment or accumulation of a drug in a patient with pre-existing renal disease.

Aciclovir	Ifosfamide
Aminoglycosides	Lithium
Amphotericin	Mannitol
Cisplatin	NSAIDs
Contrast media	Paracetamol
Ciclosporin A	Tacrolimus
Ethylene glycol	Vancomycin
Foscarnet	

Renal replacement therapy should be commenced in cases of severe hyperkalaemia, intractable fluid overload, metabolic acidosis, and overt uraemia accompanied by pericarditis or uraemic bleeding. Haemodialysis, peritoneal dialysis and haemofiltration can be used in patients with ARF. Haemodialysis, usually through a central venous catheter, can only be used in haemodynamically stable patients, whereas peritoneal dialysis is generally less applicable. Haemodynamically unstable patients and those with multi-organ failure tend to tolerate intermittent haemodialysis poorly. The development of continuous haemofiltration and haemodiafiltration techniques has provided a means to give effective renal replacement therapy to such patients, and they are now standard in the majority of ICUs.

FUTURE DEVELOPMENTS

Cells damaged by a nephrotoxic stimulus can die, survive or enter a suspended state in between, depending on which genes are activated. The three pathways appear to be promoted by growth factors. Conversely, oxidative stress, tumour necrosis factor,

lipopolysaccharide and ischaemia encourage cell death. Work is ongoing to find ways of encouraging cells to take the survival pathway. When a tubular cell is assaulted by a nephrotoxin, one of three things can occur — the cell can die and be lost into the tubular lumen, it can be trivially injured and recover quickly with no evident effects, or it can be seriously injured. The cell can then proceed down one of two pathways depending on the activation of different genes. The challenge, therefore, is to develop agents that can be administered exogenously to encourage survival gene expression, rather than allowing death pathway gene transcription.¹²

A number of agents have showed great promise in animal studies at encouraging recovery from, and protection against, acute tubular necrosis. These include insulin-like growth factor and atrial natriuretic peptide. Unfortunately, when tested clinically, neither of these agents was effective.^{13,14} Other agents that can be useful therapeutically are anti-ICAM-1 (intercellular adhesion molecule-1) antibodies, arginine-glycine-aspartate peptides and antioxidants.

OUTCOME

ARF is a life-threatening condition, with a mortality rate of about 40 per cent.¹⁵ Out-

come depends on pathogenesis. If the cause is obstruction which is successfully relieved, or acute tubular necrosis, in which haemodynamic parameters return to normal quickly, then recovery approaches 100 per cent. However, if ARF arises from glomerulonephritis, the prognosis depends on the severity of damage.

Damage might be irrecoverable if too many glomeruli are involved. In such cases, the patient will need to remain on dialysis permanently.

CONCLUSION

ARF is common in hospitalised patients and is most often caused by acute tubular necrosis. It is associated with significant mortality and morbidity, and is an expensive disease to treat.

Drugs play an important role in the pathogenesis of ARF. Pharmacists, therefore, can make a major contribution to the care of patients with acute renal failure by identifying possible pathogens, by ensuring that patients do not receive any further nephrotoxic compounds during the recovery phase, and by advising on appropriate dose adjustments for drugs given to patients while undergoing renal replacement therapy.

PANEL 5: DRUGS THAT CAUSE INTERSTITIAL NEPHRITIS

Acute interstitial nephritis is a hypersensitivity reaction. Most cases follow drug exposure, although in some cases the cause is unknown, but it can be a complication of infection.⁷

The clinical picture includes a fall in GFR, eosinophiluria and white cell casts with variable proteinuria and haematuria. In some cases of drug-induced interstitial nephritis, extra-renal manifestations of allergy can be present, eg, fever, rash, arthralgia, and abnormal liver function tests.

Allopurinol	Furosemide	Penicillins
Aminosalicylates	Gold	Phenytoin
Bumetanide	Interferon	Quinolones
Cephalosporins	Isoniazid	Rifampicin
Cimetidine	Lithium	Sulphonamides
Cotrimoxazole	NSAIDs	Thiazides

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