Acute renal failure and the critically ill surgical patient

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ABSTRACT

Acute renal failure can occur following major surgery. Predisposing factors include massive haemorrhage, sepsis, diabetes, hypertension, cardiac disease, peripheral vascular disease, chronic renal impairment and age. Understanding epidemiology, aetiology and pathophysiology can aid effective diagnosis and management. A consensus definition for acute renal failure has recently been developed. It relates to deteriorating urine output, serum creatinine and glomerular filtration rate. In the surgical patient, precipitants are often pre-renal, although intrinsic damage and obstructed urine flow can occur. Worsening renal function results in distal organ damage. Acute renal failure is a marker of disease severity, carrying a poor prognosis if associated with deteriorating respiratory and cardiovascular function. Acute renal failure in the critically ill surgical patient exerts a massive impact on the evolution of complications and prognosis. Management relates to treating life-threatening problems, maintaining effective ventilation and circulation, removal (or reduction) of nephrotoxins and, where appropriate, establishing either renal replacement therapy or palliative care.

KEYWORDS

Acute renal failure – Intensive care – Renal replacement therapy – surgery

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Acute renal failure (ARF) can be described as a sudden sustained fall in glomerular filtration rate (GFR) associated with accumulation of metabolic waste products and water. It is a major postoperative complication in surgical patients with a quoted incidence of 10–25%.^{1,2} Predisposing factors include severity of physiological insult, pre-existing comorbidity, hypovolaemia and sepsis. Despite improvements in recognition and management, *e.g.* renal replacement therapy (RRT), mortality remains high.⁵ This high mortality and a variety of definitions warrant further attention if understanding of ARF and improvements in management are to develop. Such attention focuses on definitions, epidemiology, aetiology and pathophysiology.

Definitions

Several definitions exist. The British Renal Association defines ARF as a serum creatinine > 300 µmol/l (> 3.3 mg/dl) and/or a blood urea nitrogen value > 40 mmol/l (240 mg/dl) with previously normal values. The critical illness scoring system, APACHE III, defines ARF as a serum creatinine elevation > 136 µmol/l per day (> 1.5 mg/dl), with a urine output < 410 ml/day and no pre-existing chronic

dialysis.⁴ One review of ARF found 26 different definitions of postoperative ARF in 26 studies.⁵ This absence of consensus reflects the condition's complexity. Definitions tend to emphasise individual factors such as biochemistry, pre-existing impairment, resuscitation measures, nephrotoxic drugs and pathophysiology,⁴ with most having common elements, *e.g.* serum creatinine and urine output.

In terms of achieving an easily applicable definition, there is logic in this as they are functions virtually unique to the kidney, easily and routinely measured. Other biochemical criteria such as raised urea, hyperkalaemia and acid-base disturbance are more open to influence from extra-renal factors, *e.g.* gastrointestinal bleeding, trauma, burns, and endocrine disturbance. This issue is now reflected in a new consensus classification from the *Second International Consensus Conference of the Acute Dialysis Quality Initiative*.⁶ The acronym RIFLE stands for Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal disease. It is a multilevel classification (Fig. 1) permitting incorporation of a wide range of progressive disease processes and spectra. It also incorporates factors considered pertinent to ARF (*e.g.* pre-existing renal disease, rate of

GFR criteria		Urine output criteria
Risk	Increased creatinine $\times 1.5$ from baseline 25% reduction in GFR	< 0.5 ml/kg/h over 6 h
Injury	Increased creatinine $\times 2$ from baseline 50% reduction in GFR	< 0.5 ml/kg/h over 12 h
Failure	Increased creatinine $\times 3$ from baseline 75% reduction in GFR	< 0.3 ml/kg/h over 24 h
Loss	Persistent ARF. Complete loss of kidney function for > 4 weeks	
ESRD	End-stage kidney disease (> 3 months)	

Figure 1 RIFLE classification for acute renal failure.⁶

functional deterioration) combining them with a stratification based on levels of urine output and serum creatinine. It is readily usable and clinically applicable across patient groups.

Its limitations should, however, be recognised. Serum creatinine can overestimate renal function during the initial development of renal failure – trauma, fever and immobilisation all increase creatinine production and liver dysfunction and decreased muscle mass reduce creatinine production.⁷ Urine output can vary depending on factors extrinsic to the kidney including post-surgical endocrine changes and post-renal obstruction.

Epidemiology

Lack of consensus definitions, with heterogeneity of patients and disease processes, account for the reported variability in epidemiology. The frequency of ARF among all patients on hospital admission is estimated at 1%.⁸ ARF associated with surgery being the second most common cause of ARF identified.⁸ Approximately one-third of patients developing ARF require critical care admission.⁹ In the largest study to date, patients with ARF on the intensive therapy unit (ITU) had an overall mortality of 62%,¹ longer ITU stays, higher APACHE III scores and lower survival rates.^{10,11}

ARF is, therefore, a marker for severity of illness and, with respect to any individual organ system, arguably the strongest denominator for survival in critically ill patients.¹¹ Relative to patients with the same severity of illness (*e.g.* as judged by APACHE II), it carries between 4.0 (homogeneous critically ill patients) and 7.9 times (cardiac surgery) mortality on intensive care.^{1,12} Patients with ARF not requiring RRT have a mortality rate of 15%, as opposed to 62% in those

requiring RRT.⁹ Such high mortality rates are, in part, due to evolving trends in patient demographics. *e.g.* more invasive surgery in older patient groups with significant co-morbidities¹⁵ that may conceal improvements in hospital (52% versus 32%) and 1-year (30% versus 21%) survival rates plus renal recovery rates (96% versus 78%) cited over the past 30 years.¹⁴

Predisposing factors

Suggested predisposing factors include pre-existing renal impairment, hypertension, cardiac disease, peripheral vascular disease, diabetes mellitus, jaundice, age, massive haemorrhage and severe sepsis.^{2,8} In the context of surgical patients, absence of uniform definitions and complex interactions between different risk factors has resulted in limited evidence for the relative contribution of such risk factors to ARF.

Pre-existing renal impairment has been implicated as the most significant pre-operative factor contributing to ARF,¹⁵ with risk inversely related to creatinine clearance.¹⁶ Compared to patients with previously normal renal function, those with pre-existing renal impairment have increased morbidity and mortality manifesting as increased inotrope usage, number of ventilated days, prolonged intensive care and overall hospital stay.¹⁷

The incidence of dialysis-dependent ARF depends on the nature of surgery, and ranges from 1% post coronary artery bypass surgery¹⁶ to 50% in some series of thoraco-abdominal aortic aneurysm surgery.¹⁸ Increasing age has also been identified as a risk factor, although this factor in isolation should not preclude patients from treatment.⁵ Age-related predispositions include reduced renal reserve, susceptibility to volume depletion due to a 'thirst deficit', and reduced ability to conserve salt and concentrate urine.¹⁹

Aetiology in the critically ill surgical patient

For diagnostic/aetiological purposes, ARF has historically been divided into three distinct entities determined by basic pathophysiology (Table 1) – pre-renal, renal or intrinsic and post renal or obstructive. These account for 30–60%, 20–40% and 1–10% of cases in the surgical setting, respectively.¹⁵ In the critically ill patient, the initial insult is usually pre-renal with renal hypoperfusion from either vasodilation in severe sepsis, or hypovolaemia, *e.g.* following massive haemorrhage. This is in contrast to intrinsic damage from renal disease (*e.g.* glomerulonephritis) or chemical/pharmacological injury. Clinical history often indicates this basic pathophysiology but urinary biochemistry can also be used to distinguish between pre-renal and intrinsic damage, with the pre-renal damage reflecting hypoperfusion and the attempt to conserve water and electrolytes, particularly sodium (Table 2). With respect

Table 1 Causes (with examples) of acute renal failure in the critically ill surgical population*Pre-renal*

- Hypotension: sepsis
- Hypovolaemia: dehydration, blood loss, acute pancreatitis
- Reduced cardiac output: cardiac tamponade
- Intra-abdominal compartment syndrome

Renal

- Acute tubular necrosis
- Drugs: aminoglycosides, non-steroidal anti-inflammatory drugs, radiographic contrast medium
- Toxins: endotoxins
- Hepatorenal syndrome
- Intra-abdominal compartment syndrome
- Pigment nephropathy (myoglobinuria): major burns, critical limb ischaemia, major crush injuries

Post-renal

- Ureteral obstruction: stones, surgical, traumatic
- Bladder dysfunction: traumatic
- Urethral obstruction: traumatic/prostatic hypertrophy

to pre-renal failure however cellular damage (and possible tubular obstruction) may subsequently occur.

In critical illness *per se*, it is also increasingly accepted that initial aetiologies can determine the course of a disease process, *e.g.* acute respiratory distress syndrome (ARDS) from extrapulmonary causes such as sepsis behave differently to those with an intrapulmonary cause such as aspiration or lung contusion.²⁰ The analogy is potentially applicable in ARF, and supported by the fact that the mortality in patients with ARF secondary to acute tubular necrosis (ATN) has been reported as 64%, compared with 16% for those patients with ARF as part of a multisystem disease.³ This stresses the importance of not only identifying, but effectively treating the causes of ARF.

Pathophysiology

In the surgical patient, hypoperfusion is frequently the pre-renal precipitant, *e.g.* hypovolaemia, severe sepsis, cardiogenic shock, cardiac tamponade and hepatorenal syndrome (HRS). Total renal blood flow (1–1.5 l/min) normally exceeds the organ's oxygen requirements but only 10% of it passes through the renal medulla, where PaO₂ is 8–15 mmHg (1.2–2.2 kPa). Metabolically active medullary cells are, therefore, susceptible to hypoperfusion and subsequent hypoxia.²¹ Hypoperfusion initially results in afferent arteriole dilatation, efferent arteriole vasoconstriction and expansion of intravascular volume with the aim of maintaining glomerular

filtration. Neural and hormonal factors (including the renin–angiotensin–aldosterone system) mediate this response. Left unabated, vasoconstriction results in ischaemia. HRS is a classic example of the consequence of this cascade of events; intense vasoconstriction of the renal circulation occurs in response to extreme under filling of the arterial circulation, due to arterial vasodilatation in the splanchnic vascular bed.²²

Ischaemia-reperfusion injury²³ can arise either after circulatory restoration from global hypoperfusion or in isolation, *e.g.* aortic cross-clamping in vascular surgery. Whilst mechanisms remain poorly understood, ischaemia results in vasoconstriction, tubular swelling and endothelial activation. In the post-ischaemic reperfusion period, activated neutrophils generate and release reactive oxygen species and cytotoxic compounds. Surrounding tissues are infiltrated, circulating polymorphs and the arachidonic acid cascade are activated²⁵ worsening the inflammatory response, supporting the 'injured kidney' theory of the kidney as a pro-inflammatory mediator.

Sepsis is another major contributor to ARF in the surgical patient.²⁴ Bacterial pro-inflammatory factors and resultant cytokine release not only cause local tissue injury, but aggravate haemodynamic instability. Thus in the context of the critically ill these mechanisms are interlinked in their propagation and effect.

With respect to the histological picture in the critically ill, there is limited information.²⁵ It has been postulated that, in sepsis, malfunction arises through immune-mediated cellular apoptosis.²⁵ Post mortem evidence does not support this.²⁵ The hypothesis is also countered by patients who recover normal function in a number of days, far quicker than the regenerative capacity of renal tubular cells. Rather

Table 2 Differentiation between pre-renal and intrinsic renal damage

Investigation	Pre-renal	Intrinsic renal
Urinary specific gravity	>1.020	<1.010
Urinary sodium (mmol/l)	>500	<350
Urinary osmolality (mosmol/l)	<20	>40
Urine/Plasma osmolality	>2	<1.1
Urine/Plasma urea ratio	>20	<10
Urine/Plasma creatinine ratio	>40	<20
Fractional sodium excretion	<1	>1
Renal failure index	<1	>1

Notes:

Fractional sodium excretion = $\frac{\text{urine/plasma sodium ratio}}{\text{urine/plasma creatinine ratio}} \times 100$

Renal failure index = $\frac{\text{urine sodium}}{\text{urine/plasma creatinine ratio}} \times 100$

Table 3 Systemic effects of acute renal failure*Uraemic intoxication*

- Metabolic derangement: carbohydrates, lipids, amino-acids/proteins
- Endocrine abnormalities: insulin resistance, hyperparathyroidism
- Metabolic acidosis

The 'injured' kidney: a pro-inflammatory mediator

- Increased release/impaired catabolism and elimination of cytokines
- Activation of immunocompetent cells
- Release of factors promoting distal organ injury

than 'programmed cell death', an alternative mechanism may revolve around 'cellular shutdown' termed cytopathic hypoxia.²⁶ Here, outcome correlates with mitochondrial genotype.²⁷ The inherited inability to utilise oxygen at the mitochondrial level may exert a protective effect, and has been termed 'aestivation'. This concept fits well with the apparent paucity of histological changes seen at a renal tubular level, and accounts for disparities between renal biopsy results and clinical severity.²⁵ It may also account for the rapid restoration of renal function in some critically ill patients.

Irrespective of mechanisms involved and the absence/presence of abnormal histopathology, renal failure has systemic effects, playing a crucial role in inflammation and the evolution of distal organ injury (Table 3). If ARF develops a vicious cycle of renal dysfunction, cytokine release, dysfunction of distal organs, failure of urinary cytokine clearance and further distal organ dysfunction ensue.²⁴

Such pathophysiology creates 10% mortality from ARF alone, rising to 45–50% if associated with respiratory failure.²⁸ If three or more organ failure ensue (one of the organs being ARF), it can increase to 95%. Nevertheless 70% of survivors recover to normal renal function and less than 10% require long-term renal replacement therapy (30% if patients had pre-existing renal disease).^{9,29}

Management of ARF

Initial resuscitation – 'ABC'

Initial management rests with managing life-threatening problems and treating the cause. On-going management relates to maintaining adequate ventilation with effective circulating volume and cardiac output in order to restore renal perfusion pressure. Early transfer to critical care for invasive cardiovascular monitoring is likely. Frequent monitoring of urea and electrolytes is also necessary to gauge both the effectiveness of management and the evolution of the ARF. Obstruction to the lower urinary tract should always be excluded and, in postoperative abdominal surgical patients, intra-abdominal hypertension must be considered a contributing factor.^{30,31}

Table 4 Emergency management of hyperkalaemia ($K^+ > 6.5$ mmol/l)**Treatment**

- Airway/Breathing/Circulation
- Calcium resonium: 15 g 6–8 hourly or 30 g rectally (ion exchange resin)
- Insulin (10–20 units actrapid) in 100 ml 20% dextrose i.v. over 30 min (transiently 'drives potassium into the cell')
- Sodium bicarbonate 50 mmol i.v. over 5–10 min (exchanges potassium ions for hydrogen ions across the cell membrane)
- 10% calcium gluconate i.v. (5–10 mmol) as physiological antagonist of potassium (immediate but transient effect)
- Beta-2 agonist, e.g. nebulised or intravenous salbutamol: increases cellular uptake of potassium

Notes*Recognise effects*

- Nausea, vomiting, diarrhoea, muscle weakness
- ECG changes: peaked T waves, absent P waves, widened QRS, ventricular arrhythmias (including VF $K^+ > 7$ mmol/l), cardiac arrest

Identify surgical causes

- Increased potassium intake, e.g. rapid blood transfusion, excess supplementation
- Decreased renal output of potassium, e.g. aminoglycosides, angiotensin-converting enzyme inhibitors, potassium-sparing diuretics
- Increased movement of potassium out of the cell, e.g. acute rhabdomyolysis, major burns, crush injuries, critical limb ischemia, acute acidosis

Table 5 Indications for renal replacement therapy

Indication	Proposed value
Anuria/oliguria	Urine < 200 ml per 12 h
Hyperkalaemia	K ⁺ > 6.5 mmol/l
Severe acidaemia	pH < 7.1
Increased creatinine	Creatinine > 300 µmol/l
Uraemia	Urea > 30 mmol/l
Fluid overload	Respiratory impairment
Temperature control	Control of hypo- and hyperthermia
Sepsis	Potential: overall mechanism uncertain
Acute poisoning	Seek toxicology advice, e.g. salicylates

Effective, early management may minimise severity, allowing for natural reversal of pathophysiology. Examples include aggressive surgical control of bleeding, radiological or surgical drainage of a septic focus, and abdominal decompression to prevent abdominal compartment syndrome.

Aside from treating the immediately life-threatening causes of ARF (e.g. massive haemorrhage), immediate life-threatening consequences of ARF also require attention, *i.e.* hyperkalaemia (K⁺ > 6.5 mmol/l). This may compound acute renal failure in major burns, critical ischaemia with rhabdomyolysis and in crush injuries.³² Due to life-threatening cardiac compromise, immediate treatment of hyperkalaemia should be instituted. In certain circumstances, renal replacement therapy although indicated may not be readily available, or establishing it can waste valuable time. It is therefore essential that the resident surgeon is aware of the initial pharmacological options (and mechanisms of action) for hyperkalaemia involving calcium, dextrose, insulin, *etc.* (Table 4).

Treatment modalities

To date, with the possible exception of the use of *N*-acetylcysteine in radiocontrast-induced renal failure,^{33,34} there is no pharmacological 'magic bullet' preventing or reversing acute renal failure. Drugs such as dopexamine augment cardiac output and may have a role in restoring perfusion, although its renoprotective qualities remain uncertain.^{35,36} Low-dose dopamine has no renoprotective effect; data suggest it neither maintains nor improves renal function.³⁷ Loop diuretics are commonly used in volume control, and have a theoretical benefit of reducing metabolic demand, hence protecting against ischaemic injury. Beyond experimental models, renal protection has never been demonstrated and their use may be associated with increased mortality in ITU patients.³⁸

Nephrotoxic agents

The role of nephrotoxic substances compounding the initial renal insult must also be considered. Effects include direct cardiovascular effects, tubular damage, tubular obstruction, interstitial nephritis and glomerulonephritis. Of particular relevance to surgical patients are hypotensive agents, non-steroidal anti-inflammatory drugs, aminoglycosides and radiocontrast media. Wherever possible, such substances should be avoided. If they are necessary, plasma levels may have to be monitored and advice sought on their administration.

Renal replacement therapy

Of ITU patients with ARF, 50–70% require renal replacement therapy (RRT).¹¹ It simplifies fluid and nutritional management and early use may improve outcome.¹⁴ Indications (Table 5) for commencing renal replacement therapy can border on the subjective as no consensus currently exists⁶ although application of the

Table 6 Continuous veno-venous haemofiltration and haemodialysis

Continuous veno-venous haemofiltration	Haemodialysis
Convection: water pushed across membrane . and solute follows	Diffusion: solutes follow concentration gradient. Fluids: counter-current mechanism
'Continuous': interruptions for surgery and other procedures	Intermittent
Cardiovascular stability	Less cardiovascular stability
Less complement activation	
Less white cell sequestration	
'Middle' molecule clearance (500–5000 Da)	Better clearance of urea/creatinine

RIFLE criteria may in future aid development of specific guidelines.⁷

Considerations relate to intermittent versus continuous (Table 6). Continuous therapies predominate in the UK where 'intermittent' usually means haemodialysis (HD) and 'continuous' continuous veno-venous haemofiltration (CVVH). Few randomised, controlled trials exist comparing the two. In the absence of haemodynamic instability, the two modalities are probably equivalent.³⁹ CVVH causes less haemodynamic instability as time is allowed for fluid to re-equilibrate between body compartments.⁴⁰ This is likely to be of relevance in a variety of surgical patients, in particular those with vasodilatory shock and capillary leak where sudden, large volume fluid movement between body compartments can create life-threatening haemodynamic changes, *e.g.* septic shock, acute pancreatitis, and fulminant liver failure. CVVH has also been advocated in sepsis due to its immunomodulatory effects by removing endotoxins and inflammatory mediators.³⁹⁻⁴¹ Its overall role in this context is uncertain.

PRINCIPLE OF CVVH

Solutes (*e.g.* urea, creatinine) are removed from the blood by convection across a semi-permeable membrane in the artificial filter (Fig. 2). Water is pushed across the membrane due to an established pressure gradient, carrying dissolved solutes with it ('solvent drag'). Solutes are cleared slowly, but efficiently, over a prolonged period. A specialised, sterile replacement fluid replaces the large volume of ultrafiltrate removed. Studies have shown that filtration rates of 35 ml/kg/h result in better survival rates in critically ill patients.⁴¹ The process is continuous except when the filter clots or a procedure needs to be performed.

Figure 2 Continuous veno-venous haemofiltration.

Figure 3 Haemodialysis.

PRINCIPLE OF HAEMODIALYSIS

Solutes are removed by diffusion across the semi-permeable membrane down a concentration gradient. Blood and dialysate fluid are circulated in a 'counter-current' fashion (Fig. 3) but, unlike CVVH, no replacement fluid is re-infused. The treatment is intermittent³⁸ with large volumes of fluid being dialysed in a period of a few hours.

Anticoagulation

All patients requiring renal replacement therapy need suitable anticoagulation (usually intravenous heparin) with regular monitoring. Prostacyclin is useful in cases of heparin-induced thrombocytopenia, or patients with coagulopathies and active bleeding. Citrate has also been used as an anti-coagulant. Pathologically/pharmacologically coagulopathic patients may not require any anti-coagulant.

Vascular access

Most current RRT is veno-venous in nature. Vascular access is via a central vein. The insertion site is, in effect, determined by the location of other central venous catheters already *in situ*. Subclavian lines are associated with higher stenosis rates of up to 90%.³⁸ This may be significant if arterio-venous fistula formation is being considered for long-term renal replacement. The internal jugular route permits greater patient mobility but may be associated with increased immediate complications. The femoral route is useful for short-term renal replacement but is associated with increased rates of infection.³⁸

Conclusions

Acute renal failure can be defined as an abrupt collapse of kidney functions, occurring in series or simultaneously. It

Figure 4 Algorithm for the management of acute renal failure (ARF)

exerts a massive impact on the evolution of complications (frequently infectious) and prognosis in the critically ill surgical patient. It carries a high mortality initially because, although often a ‘victim’ of disease processes, it progressively becomes the ‘offender’ in terms of systemic effects.

The ideal goal in management is primary prevention, although this may be unrealistic given the complex, multifactorial nature of the condition. Early identification of the ‘at-risk’ patient, maintenance of euvoemia, avoidance of nephrotoxic agents, and the pre-emptive use of *N*-acetylcysteine in patients at risk of radiocontrast-induced nephropathy are arguably the only modalities available in this context. Once ARF is established, management centres on the treatment of life-threatening problems, maintaining effective ventilation and circulation

(pharmacologically aided if necessary), removal (or reduction) of nephrotoxins, and, where appropriate, establishing renal replacement therapy. These measures should form part of a step-wise treatment algorithm when assessing and determining the management surgical patients with ARF (Fig. 4).

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