Acute renal failure on the intensive care unit

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Background

Acute renal failure (ARF) is one of the commonest complications of hospitalisation, with an overall incidence of up to 7%,[1] rising towards 15% in the intensive care unit (ICU).[2] ARF independently predicts mortality,[3] to which it contributes directly largely through 'non-renal' effects such as bleeding and sepsis.[4] Prompt action can save lives and nephrons; because of this potential reversibility it is important to differentiate ARF from chronic renal failure (CRF) (Table 1).

Acute renal failure on the intensive care unit

ARF occurring on the ICU appears to be a distinct entity. In non-ICU ARF, the kidney is usually the only failed organ and the mortality is less than 5-10%.[5,6] In contrast, ICU ARF is often associated with sepsis and with non-renal organ system failure,[7] with mortality rates of over 50%, rising to 80% when renal replacement therapy (RRT) is required.[8] Predictably, death rates increase with increasing number of failing organ systems[8] but over 65% of survivors recover renal function and discontinue dialysis.[8] ICU ARF also differs in terms of likely aetiology, with 76% (*vs* 38% non-ICU ARF) primarily due to acute tubular necrosis (ATN) (Fig 1).[7]

Acute tubular necrosis

Hypoxic tubular injury involves changes in both function[9] and morphology.[10] Recovery involves tubular cell regeneration and differentiation[11] and is associated with the activation of growth response genes and the release of growth factors.[11]

The renal failure phase of ATN generally lasts 7–21 days.[12] Recovery time depends on the duration and severity of the initial insult and the presence of further insults;[12] this may be compounded by a loss of renal autoregulatory vasodilatation that exposes the renal microcirculation to even modestly reduced systemic perfusion. Most survivors with ATN return towards their baseline level of renal function, although persistent loss of renal function is more likely in those with pre-existing CRF or prolonged ARF due to repeated renal insults.[13] Numerous pharmacological strategies, including loop diuretics and 'renal dose' dopamine, have failed to ameliorate human ATN despite some experimental success.[14–20]

Table 1. Differentiation of acute (ARF) and chronic renal failure (CRF).

Previous blood tests	Is there evidence of pre-existing renal impairment? Review old records, including general practitioners'.
Haemoglobin	Drops within 2–3 days of developing significant renal impairment – the *absence* of abnormalities is more compatible with ARF
Calcium	Drops within 2–3 days of developing significant renal impairment – the *absence* of abnormalities is more compatible with ARF
Ultrasound	Shrunken kidneys (<10 cm) with cortical scarring and reduced corticomedullary differentiation suggests CRF Normal sized kidneys do not exclude CRF (eg diabetic nephropathy, amyloid, hydronephrosis, polycystic kidneys)
Serum creatinine	Rise of 50 µmol/l/day suggests ARF A 'wandering' creatinine may occur with pre-renal ARF with changing haemodynamics
History	The finding of renal impairment after a well-defined insult (eg suprarenal aortic cross-clamping) is more likely to be ARF Longer duration of symptoms may suggest CRF

Diagnosis

A practical approach to diagnosis (Table 2) will exclude unusual causes of ARF in the critically ill. These should be considered in patients:

- who do not have a clearly defined insult
- who have other abnormal clinical features, or
- in whom presumed ATN persists beyond three weeks, despite systemic recovery and the absence of repeated renal insults.

Urinalysis

Urinalysis and urine microscopy play an important role in diagnosis. The presence of haematuria, especially with proteinuria, may indicate glomerulonephritis as well as catheter trauma or urine infection. Urine microscopy will show red cell casts, indicating glomerular bleeding. Muddy brown granular casts are highly suggestive of ATN. However, urinalysis may be relatively bland.

Urine chemistry

Urine chemistry is traditionally recommended to distinguish pre-renal ARF from ATN (Table 3), but in practice it is often diagnostically irrelevant. Haemodynamically-mediated ARF represents a continuum from an appropriate renal response (pre-renal ARF) to renal cell injury (ATN). The response to improved renal perfusion (which will not ameliorate ATN) can usually differentiate the two before chemistry results are available. One niche role may be in distinguishing the avid sodium retention of the hepatorenal syndrome from ATN, with implications for both management and outcome.

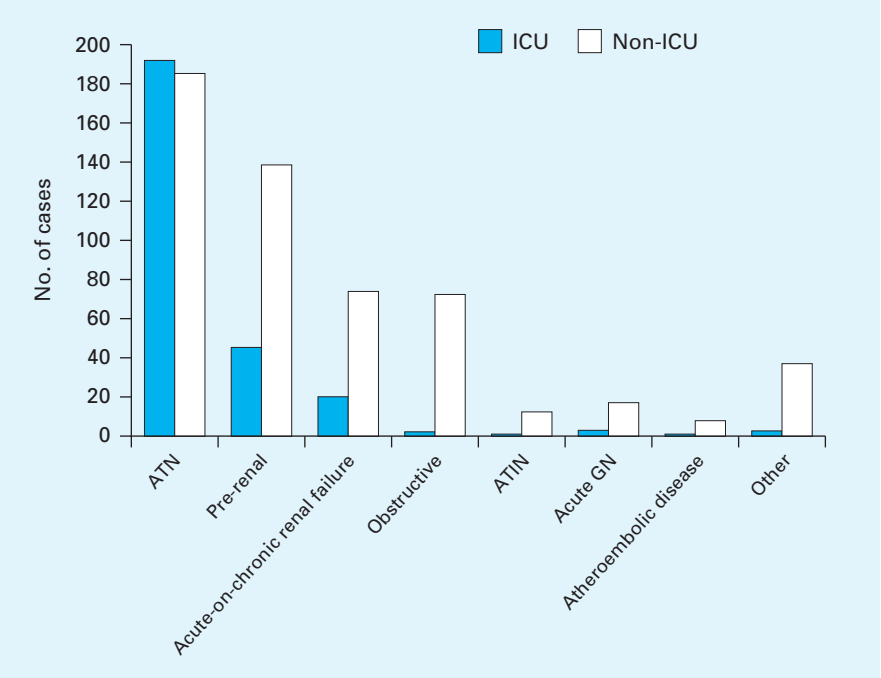

Fig 1. Spectrum of acute renal failure in intensive care unit (ICU) (253 patients) and non-ICU (495) settings. More than one type of ARF could be recorded for each ARF episode; the main ARF aetiologies are illustrated (ATN = acute tubular necrosis; ATIN = acute tubulo-interstitial nephritis; GN = glomerulonephritis (adapted from Ref 7).

Ultrasonography

The mainstay of diagnosis of post-renal ARF is ultrasonography which may be normal in early obstruction (when the renal tract is relatively non-compliant) and in the presence of ATN (the obstructed tract needs urine to dilate). Repeated scanning is recommended when there is a high index of suspicion.

Management

There are five key aspects of management of the patient with ICU ARF:

1 Treatment of the precipitating condition.
2 Optimisation of effective circulating volume.
3 Pharmacology.
4 Medical management of complications.
5 Renal replacement therapy.

Treatment of the precipitating condition

This includes the medical and surgical management of precipitants and the withdrawal of offending drugs. The possibility of post-renal ARF should be considered and treated.

Optimisation of effective circulating volume

Intravascular volume status may be assessed through:

- clinical examination
- examination of fluid balance charts
- estimation of insensible losses
- daily weights (when reliable), and
- invasive monitoring.

Table 2. A practical approach to the diagnosis of acute renal failure.

Full history

- any past history of renal disease, duration of symptoms, old blood tests
- risk factors for renal hypoperfusion:
  - vomiting, diarrhoea, bleeding, heart/liver failure, recent hypotension etc
- systemic symptoms:
  - rash, arthralgias, haemoptyses or other respiratory tract symptoms, recent infections, fevers etc
- drug history (including contrast dyes)
- recent trauma, surgery or other major illness
- history of renal stones, urinary tract symptoms

Examination

- volume status, evidence of systemic disease, urinalysis

Investigations

- urine microscopy
- full biochemical and haematological profile
- renal ultrasound
- ANCA, anti-GBM, ANA, ASOT, complement studies, myeloma screen
- consider renal biopsy (if high suspicion of treatable glomerulonephritis, allergic interstitial nephritis etc)

ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; anti-GBM = anti-glomerular basement membrane; ASOT = antistreptolysin-O titre.

Table 3. Urine chemistry in haemodynamic acute renal failure (ARF).

	Pre-renal ARF	ATN
Urine Na^+ (mmol/l)	<20	>40
Urine osmolarity (mosm/l)	>500	<350
Urine/plasma urea	>8	<3
Urine/plasma creatinine	>40	<20
FENa* (%)	<1	>2

*FENa (%) = (urine Na × plasma creatinine) ÷ (plasma Na × urine creatinine) × 100.
Urine Na^+ is less accurate than FENa as it is also affected by degree of water reabsorption.
FENa may be low in acute glomerulonephritis and early ATN.
A FENa of 1–2% is compatible with both pre-renal ARF and ATN.
Use of diuretics and dopamine may confound interpretation.
ATN = acute tubular necrosis; FENa = fractional excretion of sodium.

Fluid depletion may be obvious; if in doubt, give repeated 250 ml intravenous (iv) boluses of crystalloid/colloid boluses under continuous clinical observation. Aim for a central venous pressure/jugular venous pressure greater than 8 cm H_2O, although higher values may be needed due to high intrathoracic pressures in ventilated patients.

Effective circulating volume may require inotropic augmentation despite adequate fluid resuscitation. Bear in mind that achievement of a mean arterial pressure above 60 mmHg may still represent relative hypotension in the patient with premorbid hypertension.

Pharmacology

Avoid nephrotoxins and give drug doses appropriate to the level of renal function (check the *British National Formulary*). Both iv sodium bicarbonate and N-acetylcysteine may have a role in contrast nephropathy prophylaxis.

Medical management of complications

The widespread availability of RRT in critical care units has transformed the management of ARF. However, medical management is still important in the initial stabilisation of the patient with life-threatening complications. Fluid overload may be managed with iv furosemide (doses up to 250 mg), and a good diuretic response may be maintained with an iv infusion at a rate of 10–20 mg/hour. Daily doses higher than 1 g carry risks of ototoxicity and prolonged use in the critically ill should be avoided.[21]

Hyperkalaemia can be managed with iv infusions of calcium gluconate, dextrose and insulin, furosemide or sodium bicarbonate, although the last may result in salt loading. Nebulised salbutamol may be effective in the emergency treatment of severe hyperkalaemia but is efficacious only at doses of 10–20 mg.

Renal replacement therapy

Although RRT was first used in ARF, it is only in recent years that attention has

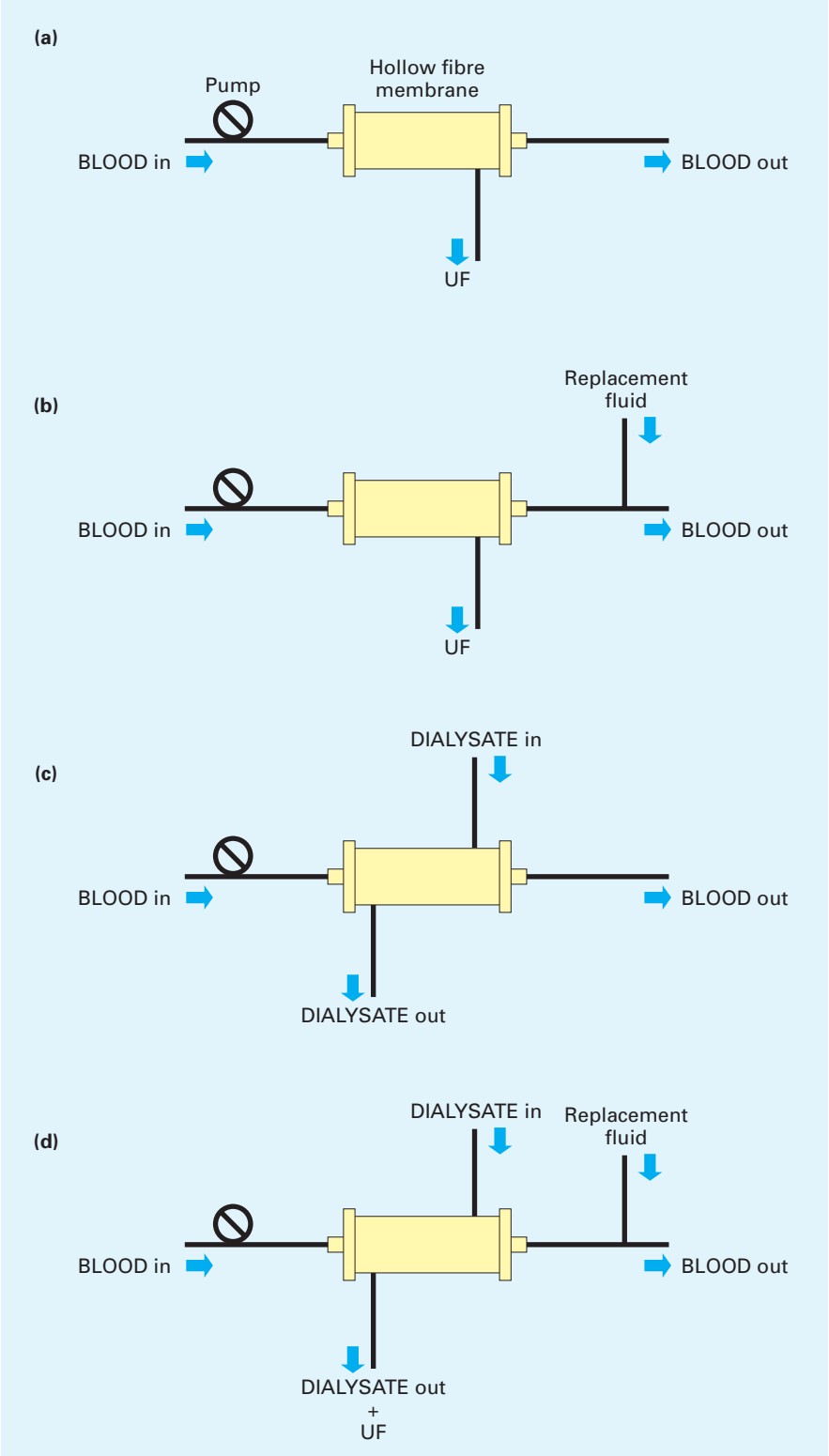

Fig 2. Diagram illustrating commonly used extracorporeal renal replacement techniques: (a) ultrafiltration; (b) haemofiltration (replacement fluid infusion may be predilutional, before blood reaches the filter, or postdilutional, after blood has exited the filter); (c) haemodialysis; (d) haemodiafiltration. Continuous arteriovenous techniques are generally pumpless (UF = ultrafiltration) (adapted, with permission, from Ref 23).

Table 4. Extracorporeal renal replacement therapy – nomenclature and use (adapted, with permission, from Ref 23).

Therapy	Definition	Use	Access	Abbreviation
Ultrafiltration	Plasma water removal, usually <5 l/day	Fluid overload CCF	AV/VV continuous VV continuous AV/VV intermittent	SCUF CVVUF IUF
Haemodialysis	Diffusion-based process using dialysate and semipermeable membrane	Azotaemia Acid/base disturbance Electrolyte balance Volume control	AV continuous VV continuous AV/VV intermittent	CAVHD CVVHD IHD
Haemofiltration	Convective-based process using plasma water exchange methods across semipermeable membrane	Azotaemia Acid/base disturbance Electrolyte balance Volume control	AV continuous VV continuous AV/VV intermittent	CAVH CVVH IH
Haemodiafiltration	Combining diffusion and convection for both small and middle molecular loss	Azotaemia Volume control	AV continuous VV continuous AV/VV intermittent	CAVHDF CVVHDF IHDF

Modalities are described according to frequency, technique and, for continuous techniques, vascular access. Continuous renal replacement therapy is an umbrella term for continuous techniques; I = intermittent; C = continuous (≡ S = slow); CCF = congestive cardiac failure; H = haemofiltration; HD = haemodialysis; HDF = haemodiafiltration; UF = ultrafiltration; VV = venovenous modality (via central venous catheter; requires blood pump); AV = arteriovenous modality (via arterial + venous cannulae; usually pumpless, systemic arterial pressure providing the driving force; now rarely performed).
This descriptive system has recently been complicated by the development of hybrids of I and C techniques, referred to as 'sustained low efficiency dialysis' (SLED), 'extended daily dialysis' (EDD) and 'slow continuous dialysis' (SCD).

again been focused on its traditional indication.[22]

RRT relies on two physical processes: convection and diffusion:

Convection. Convection involves hydrostatic plasma water removal across a semipermeable membrane (also termed ultrafiltration (UF)). Solute follows by solvent drag. High volume UF is combined with simultaneous fluid replacement (haemofiltration) to enhance solute removal and achieve a euvolaemic state (by altering removal or replacement rates). Larger solutes are removed relatively efficiently, smaller solutes (eg urea, potassium) less so, with this technique.

Diffusion. The converse applies for diffusive solute removal in haemodialysis (HD). Fluid removal in HD is achieved by the addition of a small amount of ultrafiltration. Both diffusive and (major) convective solute removal can be combined in haemodiafiltration. However, the advantages of enhanced larger molecular clearances are disputed. Firm links between RRT dose and outcome are established only for small solutes.

Figure 2 graphically illustrates the mechanics of these modalities and Table 4 describes nomenclature and use.

Many ICUs have developed experience in continuous RRT (CRRT) over the last decade.[24] This method spreads solute clearance as well as fluid removal over a much longer time frame. Intuitively, it may be seen as the modality of choice (Table 5), but there are no convincing data to suggest a superior outcome to conventional dialysis.[25,26]

The removal of inflammatory mediators during CRRT has been mooted as a potential advantage over intermittent haemodialysis (IHD). There is, however, a lack of consistent human data and a disparity between the high endogenous turnover of these mediators and their negligible extracorporeal clearance.[27]

In the absence of urgent indications for RRT (Table 6) there is no consensus over its timing of initiation.[28] An argument for early intervention before overt uraemia has developed may be countered

Table 5. Clinical considerations in the choice of continuous or intermittent forms of renal support in the intensive care unit setting (adapted, with permission, from Ref 23).

	Method of delivery	
	Intermittent	Continuous
Haemodynamic instability	Less preferable	Yes
High fluid requirements	Less preferable	Yes
High potassium generation	Yes	No
High catabolism	Yes	Yes
Global cardiac dysfunction	Less preferable	Yes
Septic shock	Less preferable	Yes
APACHE II >25	Less preferable	Yes
Bleeding*	Yes	Less preferable
Off-ward transfer (scans/surgery)	Fits in between interventions	May result in significant downtime

*Continuous renal replacement therapy generally requires continuous anticoagulation with heparin/prostacyclin to maintain blood circuit patency; intermittent haemodialysis can use saline flushes. Regional citrate anticoagulation avoids systemic anticoagulation but is a more complex and less widespread technique.

Table 6. Indications for renal support.

Fluid control	
Electrolyte balance:	Refractory hyperkalaemia
	Severe hyponatraemia
Acid-base control	Metabolic acidosis
	Severe metabolic alkalosis
Azotaemia	
Uraemic complications	Gastrointestinal upset
	Obtundation
	Encephalopathy
	Pericarditis
	Neuropathy
Other	Toxin removal

by concerns that dialysis may delay the recovery of renal function,[29] although this may be less of a problem with CRRT.[30] In practice, many ICUs commence RRT as soon as it is clear that irreversible renal failure has occurred.

Technical considerations. Certain technical considerations apply across modalities:

- The membrane material used in dialysers/haemofilters: although outcome data are conflicting, most practitioners would choose more biocompatible membranes that are less likely to promote complement and granulocyte activation.
- The choice of dialysate or replacement fluid: CRRT solutions may be lactate-based or bicarbonate-based. However, the former may not correct acidosis when hepatic perfusion and lactate conversion are impaired. IHD dialysate is now almost uniformly bicarbonate-based.

Dose. The question of what constitutes an adequate dose of RRT remains to be fully answered. Some evidence links dose with outcome,[31–33] but the optimal methods of prescribing and assessing delivery remain unclear. Dosing IHD may prove to be more complex.[34] Current evidence suggests that daily IHD may be desirable[33] and that a urea reduction ratio (100 × (1 – post-dialysis urea/predialysis urea)) above 58% is preferable.[31] For CRRT, ultrafiltration rates (for continuous venovenous haemofiltration (CVVH)), dialysate flow rates (CVVHD) or a summation of the two (CVVHDF) should be prescribed at 35 ml/hour/kg body weight.[32]

Conclusions

ARF occurring on the ICU remains a devastating condition; the predominant aetiology is ATN in the context of multiple organ failure. Its optimal management relies on the treatment of precipitating factors, optimisation of effective circulating volume and judicious use of RRT. A structured approach to diagnosis will aid in identifying more esoteric aetiologies which may require quite different management.

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Key Points

Acute renal failure (ARF) occurring on the intensive care unit (ICU) is usually caused by acute tubular necrosis (ATN) and is often associated with multi-organ failure

ICU ARF carries a mortality rate of over 50%, rising to 80% if renal replacement therapy (RRT) is required

ARF independently predicts mortality, and directly contributes to it through 'non-renal' effects such as bleeding and sepsis

65% of ICU survivors requiring RRT recover renal function

The time course of ATN is usually 7-21 days but is affected both by the duration and severity of the original insult and by the presence or absence of further renal insults

A structured approach to diagnosis helps exclude unusual aetiologies

Key aspects of non-renal replacement management include treatment of the precipitating condition, optimisation of effective circulating volume, attention to drug dosing, avoidance of nephrotoxins and conservative management of ARF complications

Continuous RRT is likely to be the best choice for the most haemodynamically unstable patients, but no renal replacement modality has yet shown superior outcomes compared with others

KEY WORDS: acute kidney failure, acute tubular necrosis, continuous renal replacement therapy, dialysis, haemodialysis, intensive care medicine

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