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Acute renal failure and renal replacement therapy in the ICU

Acute renal failure (ARF) is a sudden and sustained fall in the glomerular filtration rate (GFR) associated with a loss of excretory function and the accumulation of metabolic waste products and water. It leads to rising serum urea and creatinine, usually with a fall in urine output. Definitions such as a doubling of the serum creatinine or daily urine volumes of less than 400 ml have been used as diagnostic markers for ARF. The absence of a universally accepted definition for ARF makes determining its incidence difficult, but up to 10% of all patients admitted to the ICU receive some form of renal replacement therapy.

Patients with hospital-acquired ARF are more likely than those with community-acquired ARF to be admitted to the ICU. In critically ill patients, renal failure is often a component of multiple organ failure, and its aetiology is likely to be multifactorial. Different incidence rates between ICUs are a reflection of their case mix, as well as different attitudes to renal replacement therapy. Renal failure in patients on the ICU is unlikely to resolve with conservative management; up to 70% of patients with ARF require renal replacement therapy. In many cases, this is started within 24 hours of admission to the ICU.

The main causes of ARF (Figure 1) can be categorised as pre-renal, intrinsic or obstructive. Figure ${\bf 1}$

C	auses of acute renal failure on the ICU
Pr	e-renal (renal hypoperfusion)
•	Intravascular volume depletion (e.g. dehydration, blood loss, redistribution of fluid between body compartments)
•	Severe hypotension (e.g. sepsis, drugs)
•	Reduced cardiac output (e.g. pump failure post myocardial infarction, myocardial ischaemia)
In	trinsic renal failure
•	Acute tubular necrosis (ATN)
	Ischaemic (the extreme end of pre-renal failure, also seen with
	pancreatitis, burns, sepsis)
	Exogenous toxins (e.g. radiocontrast, nephrotoxic drugs
	- usually occurs on a background of volume depletion, sepsis
	or pre-existing renal impairment)
	Endogenous toxins (e.g. rhabdomyolysis, massive
	haemolysis, tumour lysis syndrome)
•	Hepatorenal syndrome
•	Acute glomerulonephritis/interstitial nephritis
	(with multi-system involvement)
•	Increased intra-abdominal pressure
•	Vascular (e.g. malignant hypertension, atheroembolic
	conditions)

Obstructive renal failure

Unusual to be main cause of acute renal failure on the ICU

Mortality – in the ICU, ARF alone has a mortality of 20–30% but this rises if another organ failure exists. When associated with ARF, failure of two organs leads to death in about 50% of patients, rising to over 90% if ARF accompanies three or more organ failures.

Outcome – following discharge from the ICU, about 70% of those who have developed ARF recover

renal function completely. 5–10% of patients with previously normal renal function remain on long-term renal replacement therapy. The figure is much higher (about 30%) if there is a background of pre-existing renal impairment.

Renal replacement therapies

In an ICU, renal replacement therapies can be categorised as continuous or intermittent. In the UK, continuous therapies predominate (Figure 2). There are few randomised controlled trials comparing intermittent with continuous therapies, but continuous renal replacement therapy (CRRT) is associated with reduced mortality. CRRT usually involves the removal and return of blood through a single cannula placed in a large vein (venovenous therapy); arteriovenous therapies are seldom used. CRRT causes less haemodynamic instability, because fluid removal is slower and there is time for fluid to re-equilibrate between body compartments.

Figure 2

Continuous renal replacement therapies used on ICUs			
Mode of therapy	Principal method of solute clearance		
Continuous veno-venous haemofiltration (CVVH)	Convection		
Continuous veno-venous haemodiafiltration (CVVHDF)	Convection and diffusion		
Continuous veno-venous haemodialysis (CVVHD)	Diffusion		
Slow continuous ultra- filtration (SCUF)	Fluid removal by ultrafiltration		
High flux dialysis (HFD)	Convection and diffusion		

Principles of CRRT

In CRRT, solutes are removed from blood by diffusion or convection. Different processes remove different sized molecules (Figure 3).

Figure 3

Type of molecule	Size	Example	Mode of removal
Small	< 500 Da	Urea, creatinine, amino acids	Convection, diffusion
Middle	500-5000 Da	Vitamin B,,, inulin, vancomycin	Convection better than diffusion
Low molecular weight proteins	5000-50,000 Da	β, microglobulin, cytokines, complement	Convection or absorption (on to filter
Large proteins	> 50,000 Da	Abumin	Only minimal removal by standard CRRT

Diffusion is the movement of solutes down a concentration gradient across a semipermeable membrane. This is the main physical process occurring during haemodialysis. Solutes (e.g. urea, creatinine) cross the dialysis membrane from the blood to the dialysis fluid compartment. Fluid in the dialysis compartment moves in a counter-current direction, thereby maintaining a concentration gradient. It is also possible for solutes (e.g. bicarbonate) to move in the opposite direction (e.g. from dialysate to blood).

Convection – if a pressure gradient is set up across the dialysis filter, water is pushed across the membrane and carries dissolved solutes with it; this is known as the solvent drag. The movement of fluid across the membrane as a result of this transmembrane pressure is ultrafiltration, and the fluid produced is ultrafiltrate. The process by which solutes move across the membrane is convection.

Types of CRRT

Continuous venovenous haemofiltration (CVVH) (Figures 4a and 5) is the most commonly used CRRT on an ICU, and is generally a continuous process. Solutes are not cleared rapidly, but over a continuous period are cleared efficiently. The process can be run for 24 hours a day, every day, but in practice it is often run for 24–72 hours at a time. 'Down time' occurs to change the filter (either electively or because the filter has clotted) or for procedures to take place. It is stopped when there is evidence of a return of renal function.

Blood is usually pumped through the dialysis circuit at the highest achievable flow rate (100–200 ml/minute); this depends on the quality of vascular access and the patient's haemodynamic state. A specialised, sterile fluid (replacement fluid) replaces the large volume of ultrafiltrate removed. There is no consensus on how long or how fast haemofiltration should be undertaken, but an ultrafiltration rate of at least 35 ml/kg/hour has been associated with improved survival compared with 20 ml/kg/hour. In practice, about 2 litres of ultrafiltrate are removed each hour. Either all or part of the ultrafiltrate is replaced, depending on the desired overall fluid balance.

Continuous venovenous haemodiafiltration (CVVHD) (Figure 4b) is similar to CVVH but combines diffusion and convection. Blood and dialysate fluid are circulated in a counter-current fashion. As with CVVH, a transmembrane pressure is applied, producing large volumes of ultrafiltrate. Replacement fluid is reinfused at a rate dependent on the volume of fluid to be removed.

Haemodialysis almost exclusively uses diffusion to remove solutes from plasma but can be combined with ultrafiltration to remove fluid. As with CVVHD, blood and dialysis fluid are circulated in a countercurrent fashion, but no replacement fluid is reinfused. This treatment is generally performed intermittently for patients with end-stage renal failure needing chronic dialysis. It can be performed continuously on the ICU, but its use is not widespread.

Ultrafiltration can be applied alone as a slow and continuous therapy, termed slow continuous ultrafiltration (SCUF) (Figure 4c). Ultrafiltrate is formed at a rate of less than 300 ml/hour and replacement fluid is not infused. It can be useful when there is volume overload, but no solute accumulation (e.g. congestive cardiac failure).

Continuous high flux dialysis uses a highly permeable dialysis membrane with blood and dialysate circulating in a counter-current fashion. The production of ultrafiltrate is controlled by pressure, and is reinfused by backfiltration in the blood system; therefore, a separate replacement fluid is not needed. This process is seldom used on the ICU.

Figure 4



Indications for starting renal replacement therapy

It is better to start renal replacement therapy early rather than wait for complications of ARF to develop (Figure 6). Fluid balance is a major stimulus for starting CRRT in critically ill patients because large volumes of daily intravenous fluids are required to maintain intravascular volume, and for drug delivery and nutrition.

Convection removes low molecular weight proteins of 5000–50,000 Da. Many of the septic mediators (e.g. cytokines, complement) lie within this group. These mediators are absorbed onto the filter membrane and so removed. Interest surrounds the use of high volume haemofiltration to remove these inflammatory mediators to improve outcome from severe sepsis. High volume filtration is defined as ultrafiltration of over 2 litres/hour, and there is evidence that filtrate volumes up to 6 litres/hour are associated with a significantly lower mortality in septic patients.

Figure 5: The Prisma (Hospal) continous renal replacement therapy machine. a. information screen; b. four pumps (diasylate, blood, replacement fluid, effluent); c. filter; d. effluent bag;

e. replacement fluid.



Figure 6

Indications for starting renal replacement therapy

Indication

Anuria or oliguria Hyperkalaemia

Severe acidaemia Serum urea > 30 mmol/litre or creatinine > 300 µmol/litre Refractory fluid overload

Uraemic complications

Temperature control Drug overdose Sepsis

Comments

Urine volumes < 200 ml/12 hours Serum potassium persistently > 6.5 mmol/litre pH < 7.1 Values are not absolute, only a guide Especially if compromising lung function Encephalopathy, pericarditis, neuropathy or myopathy Hyper- or hypothermia See Figure 7

Vascular access

Most renal replacement therapy is venovenous in nature; therefore, vascular access is usually via a double-lumen vascular catheter placed in a central vein. Blood is withdrawn from the proximal lumen ('arterial side') and returned through the distal lumen ('venous side').

The site of insertion is determined clinically, because critically ill patients often have other central venous catheters in place. The subclavian route is usually avoided in patients who may need an arteriovenous fistula for long-term haemodialysis, because the incidence of subclavian vein stenosis following cannulation is high.

Blood flow through the catheter should be good. Poor access should not be treated by reducing blood flow rates, because this leads to ineffective solute clearance.

Dialysis filters

As blood comes into contact with the filter (membrane) surface, complement and leucocytes can become activated, triggering the coagulation cascade and inflammatory pathways. The degree of activation is variable, with some filters having more 'membrane biocompatibility' than others (more biocompatibility means less activation). It is suggested that biocompatible membranes are associated with an improved outcome from ARF, but the evidence is not robust.

Filter membranes are either cellulose based or synthetic. Cellulose-based filters (e.g. cuprophane, cellulose acetate) are very thin and strongly hydrophilic. They are generally low-flux membranes and are poor at removing middle molecules. Synthetic filters (e.g. polysulfone, polyamide, polyacrylonitrile) are high-flux membranes and are generally more biocompatible than cellulose membranes. The flux of a membrane refers to its hydraulic permeability and how much convective transport can take place across

it. Most filters used for CRRT are synthetic, high-flux membranes with a surface area of $0.6-1.2 \text{ m}^2$.

Replacement fluid

A sterile replacement fluid replaces the ultrafiltrate removed by haemofiltration and haemodiafiltration. The fluid is infused either before the filter (pre-dilution) or into blood leaving the filter (post-dilution). Pre-dilution lowers the haematocrit of blood passing through the filter, thus reducing anticoagulation requirements, but leads to a 10% reduction in solute clearance.

The main buffers in replacement fluid are lactate or bicarbonate. Many critically ill patients already have a lactic acidosis or are unable to handle lactate appropriately. In these patients, a paradoxical worsening of the acid–base balance may be seen with a lactate buffer.

The concentration of sodium, potassium and glucose in the replacement fluid can be varied depending on the clinical need. However, the fluid does not contain phosphate or amino acids and these may have to be supplemented.

Anticoagulation during renal replacement therapy

During CRRT, blood is continually in contact with the circuit tubing and the filter, with consequent stimulation of the coagulation cascade. Recurrent clotting of the circuit renders treatment inadequate and is a drain on nursing and financial resources.

Often, CRRT can be performed in critically ill patients without the use of anticoagulants because they often have deranged clotting, thrombocytopenia or both. Anticoagulation-free CRRT is made easier with good venous access, good blood flow rates and pre-dilution.

If anticoagulation is required, unfractionated heparin at doses that do not alter the activated partial thromboplastin time (e.g. 5–10 IU/kg/hour) can be used. Full systemic heparinisation is seldom needed. Other options include low-molecular-weight heparin, recombinant hirudin, regional heparinisation and the use of prostacyclin. The latter inhibits platelet aggregation but has no effect on coagulation parameters. Its side-effects include vasodilatation, but this is seldom a contraindication, even in patients with an unstable cardiovascular system.

Pharmacokinetics on CRRT

The high-flux haemofilter membranes used in CRRT are permeable to most non-protein-bound drugs (Figure 7). While receiving CRRT, the doses of drugs should be given on the assumption that the GFR is 10–50 ml/minute. When a patient with ARF is not receiving renal replacement therapy, the GFR should

be assumed to be less than 10 ml/minute. With pre-dilution, the concentration of the drug entering the membrane is reduced by dilution. During CRRT, the highest drug clearances occur with drugs that are not protein bound or when post-dilution is used.

Figure 7

Pharmacokinetics

Drugs removed on haemodialysis

- Salicylates
- Methanol
- Barbiturates
- Lithium
- Aminoglycosides
- Cephalosporins

Drugs not removed on haemodialysis

- Digoxin
- Tricyclic antidepressants
- Phenytoin
- Benzodiazepines
- β-blockers
- Oral hypoglycaemic agents

Further reading

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