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Management of acute renal failure on the intensive care unit

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Acute renal failure (ARF) complicates up to 5% of all hospital admissions, and as many as 35% of patients admitted to an intensive care unit (ICU) receive renal replacement therapy (RRT)[1]. These figures will vary with the case mix of the unit, the threshold at which RRT is instituted and the definition of ARF used. The lack of a consensus definition of ARF remains a major problem in interpreting studies of its epidemiology, management and outcome. In ICU, ARF nearly always occurs as part of multiple organ failure (MOF) for which mortality exceeds 60%, rising to over 90% if four or more organs fail. Early diagnosis and the appropriate monitoring and timing of intervention will prevent the fatal metabolic sequelae of ARF. This article reviews the causes and management of ARF in the ICU.

Aetiology

The causes of acute oliguria and ARF may be conveniently grouped into three categories: pre-renal, renal and post-renal[2]. Post-renal failure, which results from obstruction at the level of the renal pelvices, ureters or bladder outflow tract, develops relatively rarely on ICU but may be part of the problem precipitating admission. ARF in the ICU is most commonly due to pre-renal factors, particularly systemic hypotension and intravascular volume depletion causing renal hypoperfusion, progressing to acute tubular necrosis (ATN) if appropriate treatment is delayed. Intrinsic or primary parenchymal renal disease refers to the insults directly affecting the tubules, glomeruli and the renal vasculature (Table 1).

Presentation

ARF in acutely ill patients is frequently asymptomatic. It presents with a rising blood urea and creatinine, with or without clinical or biochemical hyperkalaemia and acidaemia, and a reduced urine output. This pattern has frequently started to develop during the hours or days before admission to ICU; it is included in protocols used to identify 'patients at risk' and to 'trigger' earlier referral. Acute oliguria is defined as urine excretion of less than 400 ml/day, but in patients on the ICU, who are invariably catheterised, production of less than 0.5 ml/kg/hour for two successive hours should prompt review.

A blocked urinary catheter or the intense salt and water retention associated with critical illness may be the cause, but should not be assumed until all pre-renal factors (blood pressure, cardiac output, tissue hydration, intra-abdominal pressure) have been assessed and appropriate treatment instituted. Markedly elevated intra-abdominal pressure (>30 cmH_20) may also cause renal ischaemia. This may result from fluid accumulation and bowel distension after laparotomy or from gross ascites. Urgent measures are required for the life-threatening complications of ARF but not for urea and creatinine levels alone unless they are markedly raised (Box 1)[3].

History, examination and investigation

A history of renal disease is frequently not available from the patient, but relevant past medical history, including pre-existing renal dysfunction and recent drug history, should be sought from the family, general practitioner and hospital notes (Box 2). Clinical examination should specifically address the following questions:

1 What is the cause of the oliguria/ARF?
2 Are the blood pressure and intra-

Table 1. Acute renal failure on the intensive care unit.

	Pre-renal		Intrinsic
I	**Hypovolaemia:** • haemorrhage, burns, dehydration, gastrointestinal fluid loss, vomiting, diarrhoea, diuretics, pancreatitis, peritonitis, sepsis•	I	**Acute tubular necrosis:** • ischaemia, toxins: NSAIDs, radio-contrast, aminoglycosides, cyclo-sporin, acetaminophen, chemo-therapy, rhabdomyolysis, oxalate
II	**Low cardiac output state**: • cardiogenic shock, myocardial infarct, tamponade, tension pneumothorax, pulmonary hypertension, pulmonary embolus, cardiac arrest	II	**Diseases of glomeruli and renal microvasculature**: • glomerulonephritis, vasculitis, SLE, accelerated hypertension, HUS, DIC
III	**Renal vascular function**: • *vasodilatation*: anaesthesia, sepsis, drugs • *vasoconstriction*: noradrenaline, adrenaline • *hepatorenal syndrome*	III	**Renovascular obstruction**: • *Renal artery and vein obstruction*: atheroma, emboli, dissection, aneurysm, thrombosis and compression
IV	**Renal hypoperfusion**: • *impaired autoregulatory mechanisms* (thromboxanes, prostacyclin, endothelin)	IV	**Other**: • interstitial nephritis, infiltration, fungal, idiopathic

DIC = disseminated intravascular coagulopathy; HUS = haemolytic uraemic syndrome; NSAID = non-steroidal anti-inflammatory drug; SLE = systemic lupus erythematosus.

and extravascular fluid volumes adequate (as assessed from skin turgor and subcutaneous tissues)?

3 Is the patient fluid overloaded/in danger of pulmonary oedema?

An arterial (or even venous) blood gas sample analysed for acid-base state, lactate and potassium provides the crucial initial information that will influence the urgency of treatment.

Classically, analysis of plasma and urine biochemistry and microscopy of any urinary sediment will distinguish between pre-renal ARF, intrinsic ARF and chronic renal failure (Table 2). The urinary electrolyte patterns are affected by earlier treatment with frusemide and dopamine and are therefore potentially misleading. The urea and creatinine should be interpreted in the light of muscle mass, catabolic state, liver function, and the possibility of recent or chronic gastrointestinal blood loss which causes a disproportionate increase in plasma urea.

A chest X-ray should be reviewed for the presence of pulmonary oedema, pleural effusions and potential causes of ARF (eg pneumonia, tamponade). Ultrasound examination of the renal tract is mandatory if obstructive renal pathology is suspected; it assesses kidney size, and in the infected patient may reveal intra-abdominal foci of infection. Interventional radiological investigations may be indicated if vascular anomalies are suspected.

Management

Management of ARF on the ICU focuses on prevention of life-threatening complications of ARF, removing nitrogenous waste and providing supportive therapy until the cause of the renal failure is successfully treated and native renal function returns[4].

Monitoring

In critically ill patients, a central venous catheter and an arterial cannula are required. Further invasive monitoring to measure cardiac output and assess lung water (as derived from indicator dilution techniques) may be necessary in the patient with MOF. To avoid organ ischaemia and loss of renal autoregulation, the mean arterial pressure should be maintained above 65 mmHg, and higher levels may be necessary in patients with pre-existing systemic hypertension.

Fluid resuscitation

Fluid resuscitation to 'optimise' intravascular volume is the essential first stage in restoring and maintaining renal perfusion. The 'adequacy' of the

Complications of acute renal failure requiring urgent renal replacement therapy:

- **Hyperkalaemia**
- **Severe metabolic acidaemia**
- **Fluid overload with pulmonary oedema**
- **Urea >50mmol/l**

Key points in the patient's history:

***Comorbidity*:**
hypertension, diabetes, cardiac disease, and pre-existing renal disease may influence the assessment and management of acute renal failure (ARF)

***Pre-morbid blood pressure*:**
hypertensive patients may require a higher blood pressure to achieve adequate renal perfusion to prevent/recover from ARF

***Drugs*:**
comprehensive drug history may help to identify the cause of ARF (eg non-steroidal anti-inflammatory drugs, aminoglycosides, contrast materials and diuretics)

Table 2. Urinary characteristics seen in pre-renal and intrinsic renal failure. (The use of frusemide and dopamine will make these measurements inaccurate).

Diagnostic Index	Pre-renal	Intrinsic
Urinary sodium concentration (mmol/l)	<10	>20
Urinary creatinine to plasma creatinine ratio	>40	>20
Urine urea nitrogen to plasma urea nitrogen ratio	>8	<3
Urine specific gravity	>1.018	<1.015
Urine osmolality (mosmol/kg)	>500	<300
Plasma BUN to creatinine ratio	>20	<10–15
Urinary sediment microscopy	Hyaline casts	Muddy brown granular casts (red cells)

BUN = blood urea nitrogen.

intravascular volume resuscitation can be assessed from the response of the arterial and central venous pressure (CVP) to fluid challenges of 250 ml of crystalloid or colloid. Absolute measurements of CVP may be misleading, particularly in the ventilated patient with raised intrathoracic pressure, since apparently high values (>12 mmHg from mid-axillary line) do not exclude intravascular volume depletion. Marked 'swings' in arterial pressure with respiration in the ventilated patient and falls in arterial pressure with intravenous sedation/analgesia suggest inadequate volume resuscitation.

After restoration of the intravascular volume, the crystalloid balance (input minus urine output, amount removed via haemofilter, and allowance for 'insensible' losses) should be set daily and regularly reviewed according to extravascular fluid status, with particular reference to lung water and pulmonary gas exchange. In established ATN, oliguria may persist and progress to anuria despite these measures. In the patient with established MOF, including acute respiratory distress syndrome, it may be necessary to accept the need for RRT and avoid further intravascular volume resuscitation that may increase lung water and compromise gas exchange even further.

Specific therapies

Inotropes, diuretics and other agents may prevent renal impairment in certain situations and convert oliguric to polyuric renal failure.

Dopamine

The use of low or 'renal' dose dopamine infusions (1–3 μg/kg/min) in the treatment of ARF is controversial. After ensuring adequate fluid resuscitation, dopamine can be justified if an increase in cardiac output and systemic pressure is required together with a natriuresis. There is no evidence that it specifically enhances renal blood flow, and recent clinical trials have shown no beneficial effect on the progress or outcome of ARF[5,6].

Dopexamine

Dopexamine is also a potent β2-adrenergic and dopaminergic agonist but, unlike dopamine, has no significant α activity. It is no better than dopamine for renoprotection, but appears to be safer with regard to cardiac events following cardiac surgery.

Diuretics

Frusemide is frequently used in patients with ARF, but the trials are largely retrospective, anecdotal and poorly controlled. It is probably best given as an infusion at 1–10 mg/hour but, despite an initial increase in urine output, there is no evidence of outcome benefit[7]. Frusemide itself can cause an interstitial nephritis and impair platelet production. Mannitol has been advocated for prophylaxis in patients with rhabdomyolysis and those receiving intravenous contrast materials, but it is no more effective than volume diuresis alone.

Other strategies

1 Lowering the urine pH to 7 provides protection in rhabdomyolysis, probably by increasing the solubility of myoglobin and reducing tubular deposition.
2 Acetylcysteine infusion reduces the renal impairment following administration of intravenous contrast media in critically ill patients.
3 A synthetic form of atrial natriuretic hormone (anaritide) increases glomerular filtration rates (GFR) in animal and human studies.
4 Substances such as endothelin receptor antagonist and insulin-like growth factor-1 may find a place in the treatment of established ATN[8].

Renal replacement therapy

RRT on the ICU has developed from a technology primarily designed to treat patients with end-stage renal failure. However, neither peritoneal nor intermittent haemodialysis provides adequate RRT for the catabolic, critically ill patient. The introduction of continuous veno-venous haemofiltration (CVVHF) was a major advance in treating patients with ARF as part of MOF. High-flow filtration has also been shown to be an effective therapy for sepsis[9].

The indications for RRT are described in Table 3.

Vascular access. RRT requires the insertion of a large double-lumen catheter that permits blood to be removed and returned to the patient at flow rates of up to 200 ml/min. Catheters may have to be replaced due to occlusion, poor flow or infection. Antibiotic-coated catheters reduce infection rates, and consequently the frequency of replacement.

Haemodialysis and haemofiltration

Haemodialysis is performed for short periods (usually 4–6 hours) and requires high, pump-driven blood flow rates. It frequently results in cardiovascular instability and requires more complex counter-current diffusion technology than simple haemofiltration (Fig 1)[10,11].

Table 3. Metabolic changes indicating need for renal replacement therapy (RRT).

Reason for RRT	
Metabolic acidosis	Arterial pH <7.2 with normal $PaCO_2$
Intractable intravascular fluid overload	Fluid +++ (pulmonary oedema)
Hyperkalaemia	K^+ >6.5 mmol/l
Uraemia	Urea >50 mmol/l
Creatinine	Creatinine >500 µmol/l

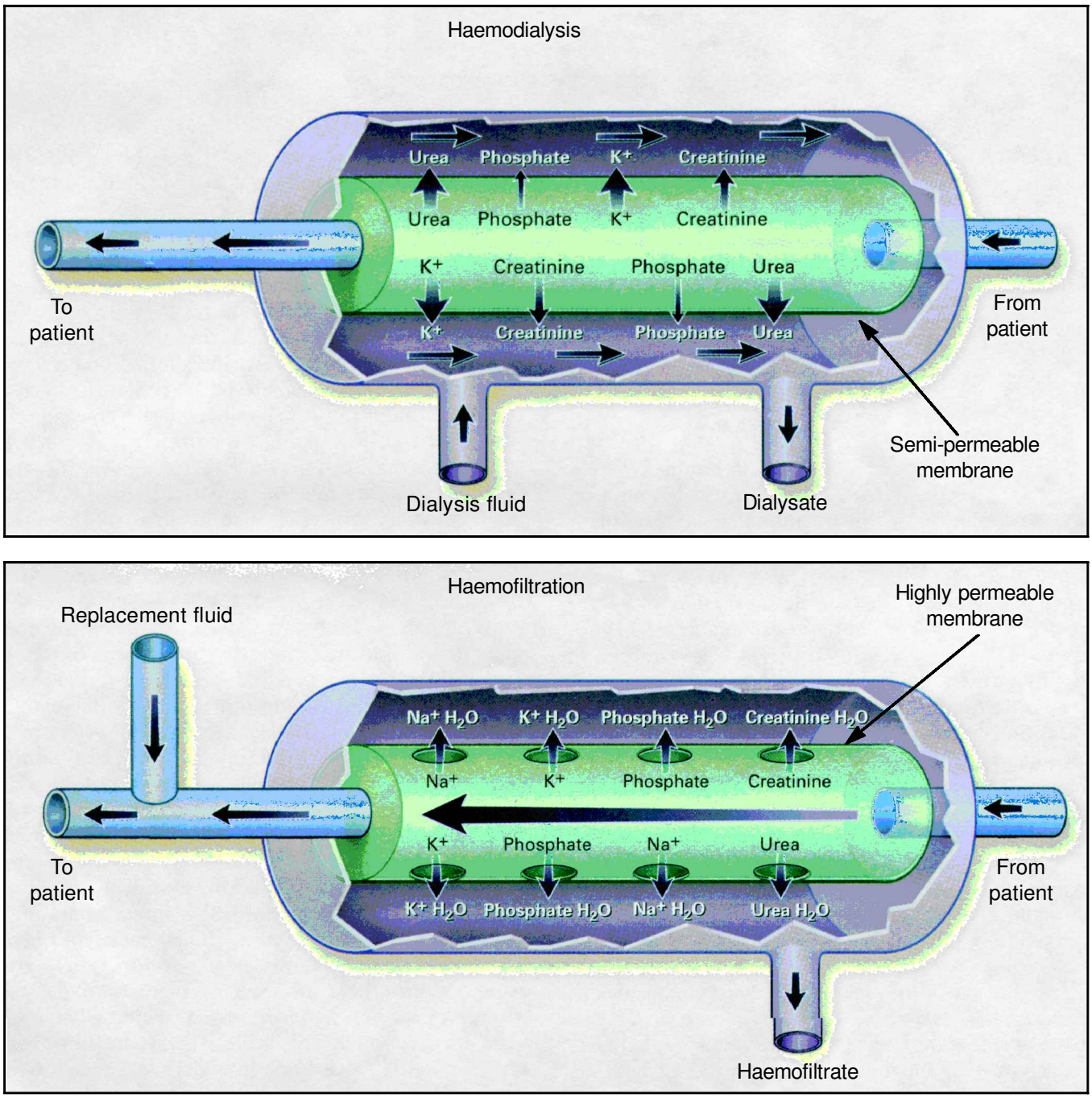

Fig 1. Diagram illustrating principles of haemodialysis and haemofiltration. Note the difference in membranes and the counter-current flow of the dialysis fluid in haemodialysis. In haemofiltration, the blood becomes haemoconcentrated during passage through the filter due to loss of haemofiltrate; replacement fluid is added after filtration to restore water and electrolyte balance. The arrows that cross the membrane show the predominant direction of movement of each solute through the membrane; the relative size of the arrows indicates the net amount of solute transferred; other arrows indicate the direction of flow. Reproduced with permission from Ref 11.

Haemofiltration is now the RRT of choice, and the most frequently used procedure in ICUs in Europe. CVVHF is a continuous process performed throughout the period of critical illness. It achieves predictable and gradual control of metabolic derangement, with little associated haemodynamic instability even at filtration rates of 60 ml/min or higher[10]. In this system, both the larger (eg heparin, myoglobin and vancomycin) and smaller molecules under 30 kDa are cleared equally efficiently. Protein-bound molecules such as sedatives (eg midazolam and its metabolites), however, are over 30 kDa and will be poorly cleared. The typical standard filtration rate of 2 l/hour is equivalent to 33 ml/min and is effectively the clearance rate or GFR achieved for molecules under 30 kDa.

Haemofiltration removes glucose and almost all ions from the plasma, including calcium, magnesium and bicarbonate. Fluid and essential molecules cleared by convection are replaced in physiological quantities by the addition of a specifically designed replacement fluid, which is added to the blood returning to the patient[10,11].

Lactate is the buffer most commonly used in the replacement fluid to correct the metabolic acidaemia. This requires conversion to bicarbonate of the infused exogenous lactate, as well as the endogenously produced lactate which occurs predominantly in the liver[12]. Typically, the serum lactate reaches a new steady state level about 2 mmol/l above the pre-filtration level. However, if the patient is generating large amounts of lactate in the tissues, and particularly if liver failure develops, the blood lactate will continue to rise and the blood pH to fall as endogenous bicarbonate continues to be removed by the filter without replacing buffer. In these situations, lactate-free replacement fluid is used and sodium bicarbonate added as a separate infusion to correct the acidaemia[13].

Precise fluid balance can be achieved: if a negative daily balance is required, more fluid is removed than is replaced and, since it is evenly removed over 24 hours, better tolerated haemodynamically. Electrolyte control is determined by the composition of the replacement fluid and the filtration rate. Since phosphate is cleared at the same rate as urea during haemofiltration (unlike haemodialysis), severe hypophosphataemia may develop and regular phosphate replacement is often necessary.

The complications that may arise with both haemodialysis and haemofiltration are listed in Table 4.

Key Points

GENERAL

- Acute renal failure (ARF) affects up to 35% of all intensive care unit (ICU) admissions
- A creatinine level above normal for sex, height and age indicates a fall in glomerular filtration rate of ≥50%
- Patients may die *with* ARF, but should not die *from* the metabolic complications of ARF
- Most patients recover pre-morbid renal function if the cause of ARF is successfully treated

HISTORY, EXAMINATION AND INVESTIGATION

- Full history with regard to drugs, pre-morbid blood pressure and renal function and other comorbidities is important
- Examination should focus on pre-renal causes and adequacy of intravascular volume
- ARF may present 'silently' with rising creatinine/acidaemia despite a normal urine output
- Patients in the ICU with urine excretion less than 0.5 ml/kg/hour for two consecutive hours are in oliguric renal failure
- Investigations should include electrolytes, arterial blood gases, urine microscopy and ultrasound scanning of renal tract
- Urinary catheter with urimeter, arterial line and central venous pressure should be monitored

MANAGEMENT

- 'Renal dose' dopamine and frusemide may convert oliguric renal failure to non-oliguric renal failure
- 'Renal dose' dopamine and frusemide have not been shown to improve mortality in ARF
- Renal replacement therapy should be started without delay to treat life-threatening complications of ARF

Veno-venous haemodiafiltration

Veno-venous haemodiafiltration combines veno-venous haemofiltration with dialysis. In theory, this allows greater clearance of the smaller molecular weight molecules, but adds complexity and expense. With the use of higher filtration rates, it offers little advantage over CVVHF and is now seldom used.

Anticoagulation

Despite the development of less thrombogenic materials, extracorporeal circuits require anticoagulation to avoid clot formation within the filter and circuit. Heparin is commonly used to 'prime' the circuit and is also infused into the blood going to the filter at rates of 500–1,000 units/hour. If thrombo-

Table 4. Complications associated with haemodialysis and haemofiltration on intensive care unit.

Central venous catheters	Trauma, haemorrhage, local haematoma, infection, occlusion, pneumothoraces, air emboli, pain
Anticoagulation	Coagulopathy, bleeding diatheses, thrombocytopenia • *Heparin*: heparin-induced thrombocytopenia • *Prostacyclin*: hypotension
HD and CVVHF	Hypotension, haemorrhage, air emboli, mechanical trauma to blood components, complement activation
Renal replacement fluid	• *Lactate buffered*: hyperlactataemia, progressive acidaemia • *Lactate free* with sodium bicarbonate infusion: hypernatraemia

CVVHF = continuous veno-venous haemofiltration; HD = haemodialysis.

cytopenia is present or complicates the use of heparin, prostacyclin and, more recently, hirudin have been successfully used[14]. Systemic coagulation and platelet count should be regularly monitored to prevent bleeding complications.

Supportive measures

Drug therapy

Drugs excreted in the urine or active metabolites that accumulate in renal failure must either be replaced by a suitable alternative or be reduced in dose and carefully monitored (eg ranitidine, digoxin, benzodiazepines, opiates, aminoglycosides and other antibiotics)[2].

Nutrition

Full calorie and nitrogen requirements for the patient should be provided. Associated problems with fluid volume and metabolic products are corrected using RRT. Commercially available formulations of enteral feed have been designed for patients in renal failure. There is some suggestion that 'immunonutritional' enteral and parenteral feeding containing 'immunonutrients' (glutamine, arginine, omega fatty acids, RNA) may reduce the morbidity associated with ARF[15].

Stress ulceration

Patients in ARF have been identified as a high-risk group for developing ulcers of the stomach and duodenum. Large meta-analyses have suggested that renal failure is an independent risk factor. This group of patients should be given stress ulcer prophylaxis, at least until full enteral nutrition is established[16].

Conclusion

Veno-venous haemofiltration provides a safe and effective method for preventing the metabolic complications associated with renal failure in catabolic, critically ill patients. It permits precise control of electrolyte and fluid balance. At high filtration rates, it may improve the outcome from severe sepsis. Patients with MOF on intensive care no longer die *from* renal failure or its treatment but *with* it and as a result of other organs failing.

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