Acute Kidney Injury Part II: renal replacement therapy

Organ specific problems

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Module Authors (update 2013)

Michael Joannidis  
Medical Intensive Care Unit, Department of General Internal Medicine, Medical University Innsbruck, Austria

Lui Forni  
Worthing Hospital, Brighton and Sussex Medical School, Western Sussex Hospitals NHS Trust, UK

Module Reviewers

Jan Frederik Bugge, Anders Enskog, Vladimir Gasparovic, Colman O’Loughlin, Liam Plant, Janice Zimmerman

Guest Editor

Rob Plant, Cork University Hospital, Ireland
LEARNING OBJECTIVES

After studying this module on Acute Kidney Injury (AKI), you should be able to:

1. Determine when renal replacement therapy (RRT) should be initiated
2. Describe the major characteristics of the available RRT modalities
3. Choose the appropriate modality for your patient
4. Consider the implications of dose prescription
5. Understand and manage the different types of anticoagulation.

FACULTY DISCLOSURES
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7 hours

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INTRODUCTION

As outlined in AKI Part I (Oliguria and Anuria), the primary function of the kidney is to eliminate the water-soluble waste products of metabolism and other potentially toxic substances such as drugs. The primary goal of renal replacement therapy (RRT) is to partly compensate for this loss of renal function and the associated sequelae. These include the accumulation of nitrogenous waste products, uraemic toxins, electrolyte disturbances, metabolic acidosis and volume overload. Importantly, the use of current extracorporeal circuits does not compensate for other endocrinological and metabolic functions of the kidney.

Reference to the website of the Acute Dialysis Quality Initiative (ADQI) will be of value to accompany this module. Furthermore, very recently the Kidney Disease, Improving Global Outcomes (KDIGO) initiative has also described guidelines for the management of acute kidney injury including renal replacement therapy.

http://www.ADQI.net
http://www.KDIGO.org


1/ INITIATING RENAL REPLACEMENT THERAPY

Absolute indications for RRT

Hyperkalaemia

Untreated hyperkalaemia is fatal and where refractory to standard measures, RRT should be initiated. A specific threshold for the initiation of RRT in hyperkalaemia cannot be recommended because this depends on the acuity of serum potassium changes and the observed physiological effects on the patient. Usually, RRT is not commenced at serum potassium values below 6.5 mmol/L where this is the sole indication.

Metabolic acidosis

Renal failure results in increasing levels of plasma organic acids and other unmeasured anions through continued fixed acid production of around 50 to 100 mmol H⁺/day. Practically, an intractable acidosis is usually considered as an indication to commence RRT although no studies exist that clearly define the threshold at which RRT is best started in metabolic acidosis with translation into clinical benefit. However, an intractable metabolic acidosis with a pH below 7.15 is a frequently quoted indication. RRT can play a major role in acid-base regulation in two ways: by the net addition of bicarbonate and by removing metabolic acids.

Volume overload

Volume overload due to salt and water retention complicates AKI in 30 to 70% of ICU patients, and is associated with a greater risk of both morbidity and mortality. Indeed, patients with AKI who remain responsive to diuretic treatment demonstrate outcome benefits - as is observed in patients exposed to restrictive fluid management in acute lung injury. The use of high-dose diuretics in this setting often leads to complications with hypernatraemia and metabolic alkalosis. However, in the presence of severe refractory volume overload per se, the initiation of RRT is appropriate. It has the added benefit that ultrafiltration by RRT removes fluid in an iso-isomolar fashion, thus minimising metabolic derangements.

Uraemia

Although the development of overt uraemic signs such as pericarditis, encephalopathy or bleeding diatheses are an indication for initiating RRT, this is rarely encountered in the ICU patient. Early symptoms and signs such as anorexia, nausea, vomiting or confusion are non-specific, however, and difficult to discriminate from the features of other pathologies present in these patients. Progressive azotemia itself may be used as an indication to start RRT for critically ill patients developing AKI, although at present no generally accepted threshold based on a definitive urea concentration exists. However, observational studies suggest that a blood urea level between 20-40 mmol/L (56-112 mg/dL) is often used as a trigger for initiation.
Other indications - severe electrolyte disorders

Severe hypermagnesaemia

Severe hypermagnesaemia, characterised by somnolence, hypocalcaemia, absent deep tendon reflexes, hypotension, bradycardia and ECG changes, is usually observed at magnesium levels of 3-5 mmol/L. In the setting of chronic kidney disease (CKD) or AKI, this represents an indication for RRT.

Severe hypercalcaemia

Severe hypercalcaemia requiring RRT is a rarity. Complications associated with this disorder may be pancreatitis, arrhythmias, neurological symptoms and AKI. Severely symptomatic hypercalcaemia with values >4.5 mmol/L not responding to standard treatment is considered an indication for RRT especially if AKI is occurring.

Severe dysnatraemia

Serum sodium levels of <115 or >160 mmol/L are quoted as indications for RRT. The severity of the clinical condition, the rate at which the disorder has occurred (e.g. is the hyponatraemia long-standing and stable) and whether there has been a response to standard medical therapy will influence the decision on whether to utilise RRT.

See the PACT module on Electrolytes and Homeostasis.

Timing

When to start RRT remains a fundamental question facing intensive care medicine practitioners and nephrologists, and the timing of RRT remains a top research priority. However, to date there is little trial evidence to guide the optimal timing of RRT for AKI.

Part of the problem is that in ICU patients, AKI is often encountered at a relatively early stage before more traditional measures of renal function, found in the chronic kidney disease population, are deranged. Therefore, classical symptoms and signs of renal failure may not be as pronounced compared to a patient developing renal failure prior to ICU admission. Consequently, the indication to start RRT in critically ill patients is frequently based in practice on very early signs of AKI, such as prolonged oliguria, rather than the conventional markers of acute on chronic kidney disease - see below as indication for RRT. In the ICU, practical considerations such as the need to administer significant volume (e.g. antibiotics, nutrition) in the face of oliguria may bring forward the initiation of RRT.

Much interest has been generated over the potential role of biomarkers in predicting the development of AKI but as yet no firm recommendations regarding what biomarker(s) are to be used can be made.


Relative/non-renal indications to start RRT

**Intoxications**

Dialysis following a serious overdose of dialysable drugs or toxins is an indication for the use of RRT. Drugs that can be effectively dialysed are characterised by their water solubility, low protein binding, low molecular weight (<500 Da) and small volume of distribution. Thus, RRT may be considered in cases of overdose or intoxication with certain alcohols (e.g. methanol, ethylene glycol), salicylate, lithium, theophylline or methotrexate.

**Temperature control**

The use of extracorporeal circuits is associated with significant blood cooling which may be beneficial in intractable hyperthermia, such as malignant neuroleptic syndrome, malignant hyperthermia and heat stroke. There are case reports and a randomised prospective study which reports a favourable outcome in patients after cardiopulmonary resuscitation when applying high volume haemofiltration with cooling. However, the advent of alternative means of cooling, either externally or by adapted central venous catheters incorporating a cooled water circuit, has superseded the use of extracorporeal circuits.


**Adjuvant in treatment of sepsis**

Severe sepsis and septic shock are associated with AKI in up to 50% of patients, although classical indicators of AKI are often not initially elevated. There remains a theoretical hypothesis that the removal of inflammatory mediators associated with sepsis could translate into patient benefit. Although an attractive argument, the only prospective randomised study investigating this question did not demonstrate any beneficial effect of RRT in severe sepsis without AKI. Indeed, some evidence suggests that early RRT in sepsis may even be harmful: consequently it cannot be routinely recommended in the absence of pronounced AKI.


In the critically ill patient with multiple organ failure, the threshold for RRT is much lower, and in such cases one is guided by the clinical picture rather than any classical trigger for commencing therapy.

Starvation or limitation of protein intake should not be used to delay the need for RRT. It is better to provide appropriate nutritional intake and intervene with RRT early.

Q. In a non-catabolic, isolated pathology patient, would a less hurried progression to RRT be justified?

A. Yes

Q. Why?

A. The rate of rise of nitrogenous waste product is much less steep (than in a catabolic patient) and may be observed for a longer time before intervention.
To maintain a steady state, the two main physical processes used to carry out the kidney functions of solute and water elimination are haemofiltration and haemodialysis.

**Haemofiltration**

This is a convective process in which a hydrostatic pressure gradient is used to filter plasma water and solute across a membrane. This fluid is then discarded. The properties of the membrane determine the size and charge of the solute that can be removed and the rate at which water will be filtered for any given driving pressure. This process mimics the function of the glomerulus.

The rate of fluid removal is determined by:

- Rate of blood flow
- Hydrostatic pressure gradient across the haemofilter membrane
- Hydraulic conductance (permeability) of the membrane
- Surface area of the membrane.

**Haemodialysis**

This is a diffusive process where blood is passed over a semi-permeable membrane which separates it from an electrolyte solution flowing in the opposite direction. The purpose of this counter current flow (contraflow) system is to maintain a waste solute concentration which is always lower on the dialysate side of the membrane, thus ensuring that a gradient persists along the entire length of the membrane. The electrolyte solution contains essential solutes present in plasma water and waste solutes are removed by their movement down a concentration gradient from plasma water into the electrolyte compartment - this fluid is commonly referred to as dialysate.
The efficiency of the process is affected by several factors:

- Rate of blood flow through the haemodialyser
- Membrane properties (high or low flux)
- Rate of flow of dialysate
- Membrane surface area.

Relationship of movement of solute by diffusion varies according to molecular weight (x-axis of the diagram below) and membrane permeability (y-axis). The diffusion coefficient is inversely related to the molecular weight of a molecule.

The three coloured lines represent this relationship as it applies in water at 37 °C and membranes of different permeability (flux). Reference molecules are shown at their respective molecular weight. All modern non-cellulose e.g. polyacrylonitrile haemofilter membranes are considered high-flux membranes.

![Diagram representing diffusion through a semi-permeable membrane on the left and convection on the right](image)

An everyday analogy to Diffusion and Convection techniques are the tea bag (‘suction’ or ‘diffusion’) and the coffee filter (‘pressure’ or ‘convection’) modes of action.

Summary of haemodialysis and haemofiltration modes of action

Renal replacement systems may rely predominantly on haemofiltration (convection) or haemodialysis (diffusion) but most systems combine the two methods.

In standard, modern practice, high-flux dialysers (incorporating non-cellulose membranes) are utilised in a continuous haemodialysis (or haemodiafiltration) circuit. It is combined with continuous ultrafiltration for fluid/volume control.
Since the spontaneous filtration occurring in the hollow fibre dialyser would be much greater than the desired fluid loss, a positive pressure is automatically applied to the dialysate compartment resulting in a significant reduction of the transmembrane pressure gradient. This in turn results in a very special pressure profile inside the dialyser. Large amounts of filtration and consequently of convective transport are maintained in the proximal part of the haemodialyser in spite of a moderate net filtration. The net fluid balance is obtained by virtue of a significant amount of backfiltration of fresh dialysate in the distal portion of the dialyser. In this mechanism, diffusion and convection are conveniently combined but higher dialysate flows (>50 mL/min) are required.

**Nomenclature of renal replacement therapy**

There is a plethora of acronyms that have been generated to describe the various techniques that have been employed. A consensus statement recommends renal replacement therapy (RRT).

RRT may be Intermittent or Continuous and is described and differentiated by the prefix I (IRRT) or C (CRRT) respectively.

It must be remembered that true continuous treatment is an aspiration and that there are many reasons (planned and unplanned) why treatment may be interrupted for variable lengths of time in caring for the critically ill.


The type of extracorporeal circuit is then described, e.g. pumped veno-venous - VV. This is followed by the method of blood purification e.g. haemofiltration - H, haemodiafiltration - HDF and haemodialysis - HD. Therefore, continuous veno-venous haemodiafiltration would be represented by CVVHDF. For more information about the nomenclature, see the following reference.

Continuous renal replacement therapy (CRRT)

Continuous veno-venous haemodialysis (CVVHD)

Haemodialysis is the traditional method of acute and chronic renal replacement therapy introduced into clinical practice by Kolff. Blood is passed, via an extracorporeal circuit, through a haemodialyser containing a semi-permeable membrane. This allows adequate exchange of small molecular weight solutes into the dialysate and hence their removal from the body. In general, haemodialysis is effective for the removal of small molecular weight solutes and becomes increasingly less efficient as molecular weight rises above a thousand daltons (see diagram under ‘modes of action’ above).

Representative values for blood flow and dialysate flow are given in the diagram below.

\[
\begin{align*}
Q_B &= 80 - 150 \text{ ml/min} \\
Q_D &= 10 - 35 \text{ ml/min}
\end{align*}
\]

Schematics describing continuous haemodialysis driven by pumped veno-venous VV (high flux) dialysis and the typical operational parameters used for this technique:

- \( P \) = pump
- \( TMP \) = transmembrane pressure
- \( Q_b \) = blood flow, \( Q_d \) = dialysate flow, effluent rate = \( Q_{d} + \) fluid removal

Clearance of solute is most rapid at the institution of treatment when the concentration gradient for solute is at its highest. Anticoagulation of the circuit is required – see Task 5.

Continuous veno-venous haemofiltration (CVVH)

Haemofiltration has found most favour in European and Australasian intensive care practice over the past 40 years. Blood is circulated through an extracorporeal circuit containing a haemofilter. Hydrostatic pressure and the factors mentioned above (modes of action) will determine the rate of fluid removal. This may be substantial
and require replacement which will be determined by the volume status of the patient and on the net fluid balance desired for the patient.

**Fluid replacement - pre-dilution or post-dilution:**

Excess water and essential solute that is lost in the filtrate needs to be replaced from a sterile source of fluid. Replacement fluid is returned to the circuit either before (pre-dilution) or after the haemofilter (post-dilution) at a rate that will maintain the desired overall fluid balance.

**Filter viability** is improved by pre-dilution as it reduces the risk of clotting in the filter by reducing the haematocrit. However pre-dilution diminishes the clearance of urea and creatinine by diminishing the concentration of both compounds in the filtered volume.

The amount of solute clearance per unit time is dependent on the volume of fluid exchanged in that time and also on the sieving coefficient of the specific solute.

According to the construction of the membrane, solute of high (up to 50 000 daltons) molecular weight can be filtered. Although there are a few reports of this being of benefit in the critically ill, there is a paucity of randomised controlled studies to confirm this.

**The filtration fraction (FF)** is a factor (other than ‘pre-dilution’) which influences the filter viability. In a normal kidney, the filtration fraction is about 20% and is affected by factors that effect the renal blood flow and glomerular filtration rate (GFR) such as catecholamines and renin angiotensin system. In continuous therapies (only relevant for CVVH and CVVHDF), the filtration fraction can be simply calculated by dividing the ultrafiltration rate (UFR - equivalent to GFR) by the plasma flow rate (Blood pump speed x 1-Haematocrit - equivalent to renal blood flow).

Therefore (1-Hct) x Blood flow rate = plasma flow (PF) rate and 
Ultrafiltration rate (UFR)/plasma flow (PF) = filtration fraction (FF).

In CRRT, a filtration fraction above 25% significantly increases clotting risk through haemoconcentration. Thus if we have a blood pump speed of 250 mL/min and a haematocrit of 0.3 then PF = 175 mL/min. In order to maintain the filtration fraction at <25% the UF rate must be set no higher than 45 mL/min (43.75 mL/min). Alternatively a higher blood pump speed can be used.

Anticoagulation of the circuit is required - see anticoagulation for RRT in Task 5.
Continuous veno-venous haemodiafiltration (CVVHDF)

This process combines the two processes of diffusion and convection by introducing a countercurrent flow of dialysate into the non-blood containing compartment of the haemodiafilter. This increases the efficiency of clearance of small molecular weight solute over that of standard haemofiltration. This technique was originally introduced to increase the limited clearance of urea and other small molecular weight solute in non-pumped arterio-venous haemofiltration systems dependent on the patient’s own circulation.

Anticoagulation of the circuit is required (see below).

Intermittent renal replacement therapy (IRRT)

Intermittent haemodialysis (IHD)

This is the standard modality of renal replacement in patients with end stage renal disease. It differs from continuous forms by using higher blood flows (usually 200–400 mL/min) and dialysate flow rates (500–800 mL/min) to achieve high urea solute clearance within a short treatment period. This therapeutic modality results in rapidly declining Urea/BUN levels during each dialysis session followed by a rebound in between. Similar oscillation can be observed for acid-base state. Since there is delayed solute removal from intracellular space, intracellular water shifts may occur and have been observed in the brain by computerised cerebral tomography (CCT). Although not unique to IHD, these characteristics can lead to disequilibrium syndrome which may occur during first treatment if high BUN or severe metabolic disturbance is present. Major symptoms include nausea, vomiting, headache, seizures and coma. Furthermore, in critically ill patients, IHD results in higher rates of hypotension, which is significantly influenced by the amount of fluid removal required during each IHD session and often prevents achievement of desired fluid balance.

To minimise the adverse effects of IHD, several groups have developed modifications of IHD settings to increase haemodynamic tolerance and avoid disequilibrium syndrome. These modifications include:

- Connecting both lines of the circuit simultaneously primed with 0.9% saline to the catheter.
- Setting dialysate sodium concentration >145 mmol/L. This may be reduced as the treatment sessions progress.
- Limiting the maximal blood flow at 150 mL/min with a minimal session duration of 4 hr.
- Setting dialysate temperature <37 °C with cooling to 35 °C in pronounced haemodynamically unstable patients. Also commencing a session using...
dialysis and continuing with ultrafiltration (UF) alone may confer better haemodynamic stability.

The major advantages of IHD are facilitated patient mobilisation and lower costs due to online dialysate production as long as IHD is performed by a dedicated ICU staff and does not require additional external specified nurses. Although a matter of preference and local practice, many would regard IHD-associated haemodynamic instability and a concern regarding its possible impact on longer term renal recovery as the main reason why CRRT has been introduced into their ICUs.


Peritoneal dialysis (PD)

This technique uses the peritoneal lining as a semi-permeable membrane to allow equilibration of solute waste with dialysate introduced into the peritoneal cavity, the volume of dialysate used being dependent upon the patient’s size (normally 2 litres in an average adult). This fluid is left in the peritoneal cavity for a period of time (‘dwell time’), then drained and replaced by fresh dialysate. Good clearance of solute can be obtained by this method but it suffers from a number of disadvantages (see below), particularly in the critically ill patient and currently is rarely used in the adult ICU although does have a role where more advanced techniques are not available. It is used more commonly in paediatric practice and one potential advantage is that it does not require anticoagulation.

Complications are:

Technical
- Perforation of viscus
- Perforation of blood vessels
- Failure to enter peritoneal cavity

Clinical
- Peritonitis
- Diaphragmatic splinting/increase in intra-abdominal pressure
- Hydrothorax
- Electrolyte disturbance
- Hyperglycaemia
Q. Although modern practice has very few situations in which peritoneal dialysis would be preferred to haemodialysis/haemofiltration, what situations might give rise to a consideration of peritoneal dialysis?

A.
- Very small children
- High risk of bleeding (e.g. intracranial)
- Failure to obtain vascular access (rare these days)
- Lack of facilities and/or ability to transfer patient to an ICU or Dialysis unit.


‘Hybrid’ technologies: prolonged intermittent renal replacement therapy

The therapeutic aims of continuous RRT are correction/maintenance of volume and acid-base homeostasis in the critically ill without undue haemodynamic disturbance. Several newer technologies have sought to achieve this aim without necessarily being continuous in nature. Lower solute clearances than by intermittent dialysis are achieved but the techniques are maintained for longer periods of time. Numerous regimens/techniques have evolved which can be collectively referred to by the umbrella term ‘hybrid therapies’. An alternative description is ‘prolonged (daily) intermittent renal replacement therapy’ (PIRRT). These techniques have various approaches which differ slightly and include techniques such as:

- Sustained low efficiency (daily) dialysis (SLEDD)
- Sustained low efficiency (daily) diafiltration (SLEDD-f)
- Extended daily dialysis (EDD)

These techniques are increasingly finding favour with many ICU practitioners routinely prescribing these modalities. Advocates claim that such techniques combine the logistic and cost advantages of intermittent haemodialysis with the theoretical therapeutic advantages of continuous replacement therapies. Most equipment is effectively adapted intermittent dialysis machines with longer session durations than conventional intermittent therapies.

4/ RRT - CHOICE AND DOSE FOR MY PATIENT

Choice

Unfortunately there are few randomised controlled studies comparing the currently available types of RRT. Most studies are retrospective case studies or observational studies fraught with the usual confounders. Several studies have concentrated on intermittent versus continuous therapies with the end points being patient survival or long-term need for dialysis. No real survival benefit can be attributed to either technique.

Several factors may determine the choice of modality. These include which technique is available, the expertise of the clinician and nursing staff, haemodynamic stability, vascular access and whether the primary need is for fluid and/or solute removal. The last factor is often an important determinant, because each of these procedures is associated with a different rate of solute and water removal. For example, volume removal is best achieved using pumped veno-venous techniques whereas in the catabolic ICU patient addition of a dialysis prescription (CVVHD) may improve metabolic clearances. Furthermore, if the aim is removal of a higher molecular weight molecule then PIRRT techniques with the employment of a high-flux membrane may be desirable.

There is as yet no clear-cut evidence of superiority of one procedure over another in the critically ill. Uncertainty also remains regarding the role of continuous versus intermittent treatment in the critically ill. Homeostasis is better maintained by continuous treatment with apparent improved haemodynamic stability but at the risk of the complications of long-term anticoagulant exposure. However, in most units the approach will be to apply the technique with which the staff have most expertise.

In situations where there is haemodynamic instability or cerebral oedema, continuous treatment is preferred to minimise sudden osmotic shifts of body water. It is also important to avoid major cardiovascular instability, which can be caused by short duration, high efficiency intermittent treatment as there is some support that this will delay renal recovery.

Modern management in the ICU is normally achieved using a pumped system to achieve adequate blood flow and therefore allows a sufficient daily exchange volume during haemofiltration/haemodiafiltration to obtain and maintain satisfactory levels of urea and creatinine. As patients recover, it is appropriate to use the most convenient method that allows proper rehabilitation. The technique of providing RRT should be tailored to the clinical situation and may change from continuous to intermittent and therefore from predominantly convective to diffusive. Any method used needs to be performed by a team skilled in its use.
Q. What are the potential disadvantages of continuous RRT?

A. True continuous renal replacement therapy suffers the potential disadvantages of:
   - Continuous anticoagulation
   - Patient immobility
   - Problems with patient transfer for investigations e.g. CT scanning
   - Hypophosphataemia
   - Loss of trace elements
   - Possible infection - associated with the non-removal of a (dialysis) CVC.

Q. What are the potential disadvantages of intermittent haemodialysis?

A. Intermittent haemodialysis suffers the disadvantages of:
   - Disequilibrium syndrome
   - Osmotic fluid shifts
   - Increased intracerebral pressure in patient with acute intracerebral abnormalities (e.g. intracranial haemorrhage, stroke, traumatic brain injury)
   - Haemodynamic instability
   - Limitations to fluid removal (due to hypotension).

Dose of RRT to be used

There is good evidence from the care of chronic patients on RRT that the delivered dialysis dose or dialysis adequacy is related to improved outcomes. The adequacy of delivered dialysis is quantified by various methods including the urea reduction ratio as well as the Kt/V (K= urea clearance of a specific dialyser, t= treatment time, V= volume of distribution for urea). However, these methods are of limited efficacy when applied to the critically ill. For example, critically ill patients are metabolically unstable with variations in urea generation. Moreover, their urea volume of distribution appears to exceed the patient’s total body-water volume and selection of a target urea is highly arbitrary, as serum urea is influenced by many factors including ethnicity, age, gender, nutrition, presence of liver disease, sepsis, muscle injury and drugs.

Clinical investigations targeting delivered dose have therefore concentrated on the amount of effluent volume normalised by the patient’s weight and procedure time as a parameter for dose evaluation. This approximation gives an easy surrogate for the dose delivered and is most accurate for CVVH, using post-dilution. The effluent flow will exceed actual dose where pre-dilution is used (by roughly 10-20%) or during CVVHD/CVVHDF when filters are deteriorating. In determining the RRT prescription, the clearance of low molecular weight molecules is but one of the variables which need to be considered. Volume balance, acid-base status, electrolyte homeostasis and nutrition are all considered part of delivering an optimal RRT dose.
There are two adequately designed and executed randomised controlled trials (RCTs) testing intermittent or extended RRT dose in AKI. Neither study showed improvement in mortality or renal recovery when the dialysis dose was increased, either by increasing the Kt/V above 3.9 weekly or by achieving a plasma urea target below 15 mmol/L (42 mg/dL). Dose prescription in continuous therapies has been helped by the evidence accrued from two large multicentre trials. The ARFTN (Acute Renal Failure Trial Network) and the RENAL (Randomized Evaluation of Normal vs Augmented Level of RRT) trials both reached remarkably consistent conclusions with regard to dose delivery during CRRT. The ARFTN study compared standard-intensity pre-dilution CVVHDF with a prescribed effluent flow of 20 mL/kg/hr to high-intensity CVVHDF at 35 mL/kg/hr. No differences in outcomes between the two study arms were observed. The RENAL study was conducted in 35 centres in Australia and New Zealand. This study compared the effects of post-dilution CVVHDF at doses of 25 and 40 mL/kg/hr on 28- and 90-day mortality rates in 1464 ICU patients with AKI, with no differences being demonstrated between the groups.

A remarkable feature of both studies was the overall apparent improvement in outcomes (48% and 55% survival) achieved relative to earlier studies. Both studies also showed that the actual delivered dose was well over 85% of prescribed which is higher than that commonly achieved in standard clinical practice. Thus, in terms of day to day practice, to achieve the currently recommended dose between 20-25 mL/kg/hr, a higher target dose may need to be prescribed e.g. 25-30 mL/kg/hr.


**High volume haemofiltration in severe sepsis/septic shock?**

Subgroup analyses and observational data showing a more rapid reduction of vasopressor requirements when targeting RRT doses higher than 40 mL/kg/hr, suggested clinical benefit of high volume haemofiltration in patients with septic shock. However, a recent (largest to date) randomised controlled (IVOIRE) trial compared 70 mL/kg/hr to 40 mL/kg/hr and could not demonstrate, although there was a power analysis issue, any survival benefit in the higher dose group.

Extracorporeal circuit

For all methods requiring an extracorporeal circuit, the preferred system is to have a pump-driven blood circuit with vascular access established by the insertion of a large double lumen venous catheter, a veno-venous circuit.

These circuits are now components of increasingly sophisticated machines that control blood flow, ultrafiltration rate and the rate of fluid replacement during haemofiltration. The machines allow the running of the circuit with appropriate safety systems and precise control of volume removal and replacement, thereby minimising the risk of the major volume errors which could occur with the older more primitive systems. They also help to control the temperature of the fluid returning to the patient and thus limit the development of hypothermia.

Vascular access

The original arterio-venous circuits (as described by Kramer et al in 1977), which required vascular access via a formal Scribner shunt or large percutaneous catheters inserted into both the femoral artery and vein, have become obsolete. It is now unusual for the extracorporeal circuit to be driven by the patient’s circulation and CAVH techniques are, in the main, historical. Currently, double lumen catheters inserted into a large central vein are considered the standard access for treatment of AKI. The establishment of satisfactory vascular access is essential for the efficient functioning of all of the extracorporeal systems. Poor vascular access and low blood flow are the most common causes of circuit clotting.

The choice of vascular access is a major determinant of circuit survival in RRT with access failure causing blood flow reductions associated with early circuit clotting. Although some in-vitro studies have demonstrated a reduction in circuit life with high venous pressures, no randomised studies are available in the critically ill. Catheter choice is influenced by several factors. According to Poiseuille’s law, flow through a catheter is related to the fourth power of its radius and is inversely related to length implying that a wide bore (13 to 14 French) and short catheter is preferable. However, central position of the catheter tip improves flow thereby dictating length. In the chronic RRT programme, best flows are obtained with the catheter tip in the right atrium. Consequently, if using a femoral vein access, the catheter should be longer (usually ≥19 cm) than when using the jugular or subclavian access (usually 19 cm). Moreover, given the importance of the internal diameter of the catheter, the choice of material is also relevant as is the position of the catheter holes. Flow through end holes is laminar, which is optimal, whereas flow through side holes is turbulent and may lead to local stagnation of blood contributing to early clotting. In addition, suctioning of side holes against the vessel wall may impair flow which is not found with end holes.

Flow through the catheter is also related to patient characteristics. A low central venous pressure has been shown to be associated with catheter dysfunction and kinking of the catheter may impair catheter flow. Finally, catheter lifespan is increased through use of controlled saline infusion or by locking with heparin or citrate solutions to prevent fibrin adhesion when not in use.

Passive, patient driven extracorporeal circuits are generally unsatisfactory and rarely used.
**Priority of vascular access**

Generally, there are three major routes for access: internal jugular, subclavian or femoral vein. Subclavian access has an enhanced risk of kinking and of stenosis with longer catheter utilisation. Therefore, the right internal jugular route is the preferred point of access using ultrasound-guided technique to reduce complications. The femoral vein is also considered a safe access; however, femoral access is regarded as carrying a higher risk for infection and impairs mobilisation of patients. Consequently, the following preferences have been recommended in the KDIGO guidelines for insertion of a dialysis catheter:

- First choice: right internal jugular vein
- Second choice: femoral vein or left internal jugular vein
- Last choice: subclavian vein with preference for the patient’s dominant side.

The recommendation relating to the patient’s ‘dominant side’ or ‘handedness’ is based on the considered desirability of leaving the vein on the patient’s non-dominant side free for a permanent access device, if this turns out to be needed in time.

There is a risk of infection as is the case for any central venous indwelling catheter and attempts have been made to define an appropriate policy for catheter replacement. It has been suggested that catheter replacement on the basis of clinical indication allows for significantly fewer catheter insertions over the course of an individual’s acute RRT course, without any increase in catheter sepsis rate.

**Anticoagulation**

Due to activation of the coagulation system by the extracorporeal circuit, performance of RRT will normally require anticoagulation. The modality and amount of anticoagulation will depend on the patient and the RRT modality chosen.

**Intermittent RRT** usually requires only short courses of anticoagulation (e.g. systemic heparin bolus, repeated on requirement) or even no anticoagulation if bleeding risk is high or a severe coagulation disorder is present.
Continuous RRT usually requires continuous anticoagulation, generally done by addition of anticoagulant into the extracorporeal circuit. Alternatively, regional anticoagulation using citrate provides safe anticoagulation without increasing the bleeding risk - see below.

It is worth noting that some practitioners, likely reflecting an awareness of the heparin-associated bleeding complication rate of 10-50% described in the meta-analysis of Wu MY, 2012, use neither regional citrate anticoagulation (RCA), unfractionated heparin (UFH), low molecular weight heparin (LMWH) or prostaglandins as described below. Instead they use high blood flow and pre-dilution with good results. However, the commoner practice is to use anticoagulation as its non-use has been associated with a more rapid decline in the platelet count and if UFH nor LMWH are used in low doses as recommended in the text here, neither result in bleeding rates higher than 5%.


Minimal systemic anticoagulation

Systemic anticoagulation inhibits the coagulation cascade, platelet function or both. Low dose anticoagulation added continuously to the extracorporeal circuit is usually sufficient to keep the filter patent and mitigates the increased risk of bleeding associated with full anticoagulation.

Systemic anticoagulation

Unfractionated heparin (UFH)

UFH still is the predominant anticoagulant. Its major advantages are the low costs, ease of administration, simple monitoring and reversibility with protamine. Half-life of UFH is about 90 min, increasing to up to three hours in renal insufficiency due to accumulation of the smaller fragments. Monitoring with activated Partial Thromboplastin Time (aPTT) is still the best option although the aPTT is an unreliable predictor of bleeding. Retrospective analyses indicate increased bleeding if the aPTT is higher than 45 seconds. At this low level of anticoagulation, activated clotting time (ACT) is relatively insensitive. Given these limitations, a possible scheme for UFH consists of a bolus of 30 IU/kg followed by an initial rate of 5-10 IU/kg/hr in patients with normal coagulation. However, the level of anticoagulation should be individualised. Apart from bleeding, major side effects of UFH include the development of heparin-induced thrombocytopenia (HIT) and effects on serum lipids; also efficacy is dependent on antithrombin (AT).

Low molecular weight heparins (LMWH)

LMWH exhibit several advantages including lower incidence of HIT, lower AT affinity, less platelet (and polymorphonuclear cell) activation, less inactivation by platelet factor-4 (PF-4), higher and more constant bioavailability and lack of metabolic side effects. However, data regarding the use of LMWH in CRRT are limited. Dalteparin, nadroparin and enoxaparin have been investigated. Their mean molecular weight is
between 4.5–6 kD and mean half-life ranges from 2.5-6 hours, probably even longer in renal insufficiency. However there are indications that LMWH are eliminated by CRRT. Although some studies use LMWH in a fixed dose, continuous i.v. application of LMWH, aiming at systemic anti-Factor Xa levels of 0.25–0.35 U/mL, may be the safest option. Similar to aPTT, anti-Xa levels may not be a reliable predictor of bleeding.

**Heparin-induced thrombocytopenia (HIT)**

Depending on the dose and type of heparin, the population and the diagnostic criteria used, 1–3% of treated patients develop HIT, with the highest incidences reported for patients after cardiovascular surgery. Whenever HIT is diagnosed or suspected, it is suggested that all heparins be discontinued and an alternative anticoagulant started.

See the PACT module on Bleeding and Thrombosis.

**Platelet inhibition**

Inhibition of platelet activation by prostaglandins (PG) may be justified because the extracorporeal generation of thrombin and the use of heparin cause platelet activation. Both PGE\(_1\) and PGI\(_2\) have been investigated in CRRT, alone or in combination with heparins. The exclusive use of prostaglandins in CVVH (1.5 L/hr in pre-dilution) provided a rather short circuit survival (median 15 hr). Significant improvement of circuit survival could only be achieved when PG were combined with low dose UFH or LMWH. PGs have been successfully applied in sustained low-efficiency dialysis (SLED) as sole anticoagulant. PGs are administered in doses from 2-5 ng/kg/min. A major drawback for routine use remains their high costs and hypotension due to vasodilatation. Also PGs are not approved for use in CRRT in many countries.


**Regional citrate anticoagulation (RCA)**

Regional anticoagulation can be achieved by the pre-filter infusion of citrate. Citrate chelates calcium, decreasing ionised calcium (iCa\(^++\)) in the extracorporeal circuit. For optimal anticoagulation, citrate flow is adjusted to blood flow, targeting at a concentration of 3-5 mmol/L in the filter. Post-filter iCa\(^++\) can be used for fine tuning of the level of anticoagulation aiming at a concentration of iCa\(^++\) <0.35 mmol/L (1.4 mg/dL). Citrate is partially removed by convection or diffusion and the remainder enters the systemic circulation. Serum iCa\(^++\) is kept constant by liberation of chelated calcium when citrate is metabolised and by the intravenous replacement of calcium. As a result, systemic effects on coagulation do not occur.
Apart from being an anticoagulant, citrate is a buffer substrate. The generation of buffer is related to the conversion of sodium citrate to citric acid. Citric acid enters the mitochondria and is metabolised in the Krebs cycle, mainly in liver, but also in skeletal muscle and renal cortex, leaving sodium bicarbonate.

Citrate removal by CRRT mainly depends on CRRT dose and not on modality. Citrate clearance approximates urea clearance. The sieving coefficient, defined as the ratio of a given solute concentration to that of its plasma concentration, is between 0.87-1.0 and there is no difference between CVVH and CVVHD. Citrate removal with CRRT also depends on citrate concentration in the filter and filtration fraction; high fractions are associated with relatively higher citrate clearance and a lower buffer supply to the patient.

The use of regional anticoagulation with citrate is limited by the patient’s capacity to metabolise citrate, which is decreased if liver function or tissue perfusion are compromised. If citrate accumulates, iCa\(^{++}\) drops and metabolic acidosis ensues. In daily clinical practice, citrate measurement is hampered by the limited stability of the reagents. However, accumulation of citrate due to decreased metabolism can accurately be detected by the signs of metabolic acidosis, increasing anion gap, ionised hypocalcaemia and most specifically by an increased total/iCa\(^{++}\) concentration. Most protocols use a ratio >2.3 as an indicator for accumulation. A ratio above 2.1 predicted a citrate concentration >1 mmol/L with 89% sensitivity and 100% specificity. As shown by two recent trials (published in abstract form) citrate anticoagulation may even be safely applied in patients with liver cirrhosis as long as sufficient precautions for early detection of citrate accumulation are used.

Accumulation of citrate can also be the result of an unintended citrate over-infusion, or of decreased removal in case of a decline in membrane performance at constant citrate infusion. In these cases, ionised hypocalcaemia occurs together with metabolic alkalosis (increased bicarbonate production by citrate metabolism). Both derangements are preventable by adherence to the protocol or early detection by strict monitoring.

None of the proposed systems can attain perfect acid-base control using one standard citrate-, replacement- or dialysis solution. Requirements vary according to CRRT in use-dose variations (1.5 to 4L/hr) and whether CVVH or CVVHDF with pre- or post-dilutional methods apply. Each protocol has its own rules to correct metabolic acidosis or alkalosis and hypo- or hypercalcaemia.

Several randomised controlled studies comparing regional citrate anticoagulation to anticoagulation with either UFH or LMWH have been published generally showing longer circuit survival with citrate and less bleeding. Based on these findings, RCA may be considered a safe and efficient way of providing anticoagulation in CRRT.

Oudemans-van Straaten HM, Ostermann M. Bench-to-bedside review: Citrate for continuous renal replacement therapy, from science to practice. Crit Care 2012; 16(6): 249. PMID 23216871
Buffering agents

For chronic haemodialysis, the traditional buffer in dialysate fluid was acetate which was metabolised to bicarbonate. This caused vasodilatation and was replaced initially by lactate and eventually bicarbonate. Continuous therapies initially employed lactate as the main buffer in replacement fluid due to its excellent stability in solution. However, under certain conditions such as hepatic insufficiency, lactic acidosis may accumulate causing acidaemia due to the inability to metabolise lactate to bicarbonate.

Initial attempts to use bicarbonate as a replacement fluid buffer were hampered by stability problems. However, over the last decade several commercially available replacement fluid preparations containing bicarbonate have appeared on the market. The two major electrolytes that are not present in these fluids are potassium and phosphate. Potassium may be added according to the patient’s current blood level but phosphate is incompatible with the solution.

Serum phosphate may become significantly reduced with large volume haemofiltration or intensive dialysis and usually requires separate replacement. However, replacement solutions containing phosphate are now commercially available helping to avoid this problem. When sodium citrate is used as the anticoagulant no added buffer is required as citrate is converted into bicarbonate by the patient. Specially designed replacement fluid is available with no buffer and a low sodium concentration to compensate for the large sodium load administered as sodium citrate.

Q. What are the potential adverse effects of a low serum phosphate?

A. Severe hypophosphataemia may result in impairment of:
   - Oxygen release by haemoglobin
   - Cardiac function
   - Diaphragmatic function and perhaps weaning problems
   - Leukocyte function
   - Neurological function.

For more information on hypophosphataemia, see the following reference.
Filtration/dialysis membrane - effect on patient outcome

Older membrane materials such as the cellophane-based membranes (Cuprophan) have been shown to activate the complement system. It has been proposed that the newer membranes such as those based on polyacrylonitrile (PAN), polysulphone and polycarbonate confer a survival advantage when used in the critically ill compared with cellophane-based membranes. Studies have been published which both support and refute this hypothesis.


The newer artificial membranes allow easier passage of higher molecular weight solutes (‘middle molecules’) which seem to play an important role in the toxicity of uraemia. They also allow for a higher hydraulic conductance and high filtration rates, and are generally preferred for haemofiltration in the critically ill. High volume (approx 6 L/hr exchange) requires the use of high hydraulic conductance membranes.

For how long should RRT be continued?

Evidence from large clinical trials on RRT suggests that the mean duration of treatment is 12-13 days. Therefore, clinical practice dictates that daily assessment of both intrinsic kidney function as well as the ongoing appropriateness of RRT are required. Assessment of kidney function during RRT is not easy and also depends on the modality employed. Recovery of native kidney function can be assessed during CRRT by the serial measurement of serum creatinine as well as attention to urine output. Solute clearance of 25-35 mL/min during CRRT will result in a stable serum creatinine after 48 hours and further reduction may imply some return of native function. As the renal tubular cells regenerate and re-establish a normal tubular membrane, glomerular filtration will re-commence and urine output will increase. Increased spontaneous urinary output >500 mL/day has been described as a good predictor of successful discontinuation of RRT.

Drug dosing during RRT

Elimination of drugs by RRT depend on water solubility, protein binding, molecular weight, sieving coefficient, volume of distribution and the RRT modality and dose applied. As such no general recommendation can be given in this module. We strongly advise to consult respective drug manuals or information by the pharmaceutical companies. As a general note of caution it must be emphasised that dose recommendations given for intermittent haemodialysis are not applicable for continuous forms of RRT. With respect to antibiotics substantial underdosing has been reported during CRRT when doses recommended for IHD have been in use.

Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy 2009; 29(5): 562-577. PMID 19397464

Q. What complications can occur during haemofiltration/haemodialysis?

A:
- Vascular access
  - Vascular damage causing occlusion or haemorrhage
  - Infection
  - Insertion complications e.g. pneumothorax
- Process
  - Disequilibrium (more common with short duration intermittent haemodialysis)
  - Hypotension
  - Extracellular fluid (ECF) loss through membrane/by accident or design
  - Hypersensitivity to membrane
  - Release of pyrogens
  - Haemorrhage
  - Circuit disconnection
  - Haemolysis
  - Electrolyte disturbance
  - Air embolism

Patient outcome

The outcome for recovery of renal function is good in the vast majority of the critically ill with previously normal renal function. By six months they will normally have recovered greater than 90% of their pre-insult function. There is a small but significant incidence of non-recovery of function such that chronic renal replacement therapy is needed. This is most common in the elderly, and those with a vasculitis or pre-existing renal disease. Cortical necrosis in adults secondary to obstetric disaster is now a very rare event in western medicine.

Survival of critically ill patients with AKI is highly dependent upon the cause of the underlying acute disease and other comorbidities. The mortality for those presenting to the ICU with established AKI requiring RRT is better than for those who develop AKI at a later date despite critical care management. This latter group is usually those who have progressive multiple organ failure with its known poor outcome.

With modern forms of renal support, death from renal failure alone should not occur. Survival rates for AKI are generally reported to be around 40-50%. As organ failure involves more organ systems, the mortality rate steadily increases. It has been suggested using observational data that AKI per se has an effect on mortality.
However, as AKI is not a specific disease process but rather a syndrome secondary to other disease states it is difficult to separate the effects of the primary disease process, the length of time of the insult prior to initiation of appropriate treatment (e.g. restoration of adequate tissue perfusion) and the individual patient’s response to the primary disease from the effect of the AKI. Although scoring systems are increasing in sophistication, it is debateable whether they have achieved the discrimination necessary to resolve this issue.


Kellum JA, Angus DC. Patients are dying of acute renal failure. Crit Care Med 2002; 30(9): 2156-2157. PMID 12352064

CONCLUSION

This module is additional to the earlier Oliguria and Anuria (AKI part I) module and represents the completion of PACT’s coverage of the Acute Kidney Injury topic. It deals comprehensively with renal replacement therapies (RRT), starting with the indications and incorporating the recent KDIGO guidelines. With a strong emphasis on continuous therapies, it progresses through an understanding of the essence of the modes of therapy (dialysis and filtration) to the methods available including CVVHD, CVVH and CVVHDF. Intermittent techniques are also described and compared.

It then addresses the dosing issue and choice of dialysis technique for the individual patient before carefully talking through the important practical issues involved in providing RRT - which includes the anticoagulation (and the regional citrate anticoagulation) option, drug dosing and vascular access.

The module is set in the current environment of recent definitive randomised controlled trials, meta-analyses and consensus statements/guidelines.
PATIENT CHALLENGES

A 72-year-old woman, Mrs A, is admitted to your hospital as an emergency with a two-day history of abdominal pain of sudden onset. She has a background of hypertension and angina treated with enalapril, diuretics and a β-blocker and her exercise tolerance is normally good. Her admission pulse rate was 124 beats/min, BP 110/65 mmHg. She was noted to have peritonism and there was free gas under the diaphragm. She was taken for laparotomy after fluid resuscitation, blood cultures and antibiotics started for presumed bowel perforation.

Preoperatively her urea was 15 mmol/L (42 mg/dL) and creatinine 195 µmol/L (2.2 mg/dL). Arterial blood gases showed good oxygenation but a pCO₂ of 4.1 kPa (30.8 mmHg), pH of 7.29 and BE of −9 mmol/L.

At operation, gross faecal peritonitis was found due to perforation of the sigmoid colon which was severely affected by diverticular disease. A Hartmann’s procedure (resection of diseased colon, end colostomy and closure of rectal stump) was performed.

Learning Issues

Clinical history

Immediately after the operation, she was cold but her BP was 175/80 mmHg and her last urine output had been 75 mL/hr. However, three hours later while she is still intubated and ventilated, you are asked to see her in the recovery room with a view to ICU admission. Her pulse rate is 140/min (sinus rhythm), BP 100/60 mmHg, CVP +6 mmHg, core temperature 37.7 °C with marked vasodilatation. ST segments on her ECG trace are elevated and urinary output has been 40 mL over the past three hours and 12-lead ECG and cardiac ischaemia biomarker tests have been sent.

Arterial blood gases show: pO₂ 9.6 kPa (72 mmHg) (FiO₂ 0.5), pCO₂ 6.2 kPa (47 mmHg), pH 7.15, BE −12 mmol/L. She is receiving piperacillin-tazobactam, as broad-spectrum antibiotic treatment for peritonitis, and morphine as an analgesic.

Q. What is the initial management imperative to restore urinary output?
A. Ensuring optimal circulatory performance and thereby, optimal renal perfusion.

Q. What will your initial treatment be?
A. Fluid therapy.

Q. Why might generous fluid therapy be required?
A. To compensate for the expected large volume loss into the gut and peritoneal cavity.

Q. Will the addition of an inotrope and/or vasopressor (or further monitoring) be required?
A. It will be dependent upon the response to fluid. More advanced haemodynamic monitoring may be needed if she deteriorates further.
See the PACT module on Haemodynamic monitoring and management and the reference below.


**Learning Issues**

Restoration of the circulation

**Q. What are your goals of therapy and would you measure blood lactate?**

**A.** Reversal of the oliguria and acidosis; also of the presumed lactaeemia. Measurement (including serial review of) lactate is important to the management of this patient’s severe sepsis.

**Q. In this patient with organ dysfunction secondary to her severe sepsis but who is a known hypertensive with coronary artery disease, might you have modified goals for blood pressure and cardiac output?**

**A.** Yes. Both her renal and coronary circulation may require a higher BP than would be acceptable for an otherwise healthy person.

**NOTE** In the previously hypertensive patient a higher mean arterial pressure (MAP) may be necessary for adequate organ perfusion.

See the PACT module on Hypertension.

*Mrs A* responds well to fluids and a vasopressor (noradrenaline/norepinephrine). Her MAP rises to 90 with normalisation of her ST segments, improvement in her urinary output and correction of her metabolic acidosis. She requires a considerable volume of fluid over the next two days as her abdomen distends. On the third day her gas exchange deteriorates and despite an increase in cardiac output her perfusion pressure falls, requiring an increase in the norepinephrine support. Renal function deteriorates with worsening oliguria despite restoration of the circulation.

On examination of the patient, the colostomy stoma was found to be ischaemic in appearance. *Mrs A* was taken to the operating room for exploration of her colostomy, which was found to be devascularised to 15 cm proximal to the skin margin. The ischaemic section of bowel was removed and a new colostomy refashioned. Over the next few hours *Mrs A*’s urinary output improved and her renal function began to recover.

**Learning Issues**

Metabolic acidosis - see the PACT module on Electrolytes and Homeostasis

Secondary versus primary renal insult
Oliguria – see the PACT module on Oliguria & anuria (AKI Part I)

Underlying causes

Q. A visiting trainee asks why dopamine was not chosen in a renal dose as he has witnessed in other hospitals. What is your reaction?

A. There is no evidence from well-designed controlled studies that dopamine in low (‘renal’) dose has any effect on the recovery from or prevention of AKI. On the other hand there is evidence that dopamine may have potentially detrimental endocrine and cardiac effects.

Learning Issues

Specific treatments

Mrs A develops a methicillin-resistant Staphylococcus aureus (MRSA) infection of her abdominal wound and her respiratory tract which is treated with teicoplanin and rifampicin. At day 12 (nine days after the addition of MRSA treatment), as she is recovering from her associated respiratory failure and is being weaned from her vasoactive drugs, Mrs A develops a fever 39.6 °C, a florid maculopapular rash, neutropenia and diminishing renal function with a rising urea and creatinine.

Rash developing nine days after commencement of new antibiotics

See the PACT module on Severe infection.

Q. Other than continuing to ensure adequate renal perfusion by attention to the circulation, what should be the response to Mrs A’s further deterioration in renal function?

A. Exclude renal disease (interstitial nephritis or glomerulonephritis and renal obstruction.

Q. What a) investigative and b) other actions would be appropriate in the work-up of the renal possible pathologies mentioned above?
A) Bedside (dipstick) urinalysis and urine sediment microscopy (for renal disease) and renal ultrasound (for obstruction).

b) Request nephrological assistance according to local consultation protocol or arrangement.

Q. Presuming it is considered that there is a common cause for the fever/rash and for the renal deterioration, what would you do?
A. Search for the cause(s), including drugs, and remove or treat.

**Learning Issues**

Renal perfusion

Causes of AKI

Mrs A is found to have no circulatory deficit or urinary tract obstruction. No new infective or other occult pathological processes are discovered. Ultrasound shows enlarged echogenic kidneys consistent with AKI. Urinalysis showed 2+ proteinuria.

**Learning Issues**

Imaging
PACT module on Clinical imaging

Q. Large numbers of eosinophils were seen in the urine. What is the likely cause of the renal dysfunction?
A. A drug-induced interstitial nephritis is likely. This is not uncommonly caused by rifampicin.

The rifampicin was stopped and the MRSA infection was considered adequately treated by the teicoplanin.

Q. When you consulted the specialist Nephrology service, did you expect a renal biopsy as part of the work-up?
A. No, this would be possible if the patient’s condition permitted it but is usually foregone in the ICU when there are other diagnostic pointers and usually many relative contraindications to a biopsy - see below.
Q. After multiprofessional consultation, how would you expect the presumed interstitial nephritis to be treated?
A. Remove the offending agent and consider prednisolone as it has been suggested to improve renal function by suppressing the renal inflammatory process.

Q. Given that the evidence that prednisolone is effective is weak, are there drawbacks to the use of prednisolone that might dissuade clinicians from its introduction?
A. Steroids will increase the rate of rise of urea, and immunosuppression is a significant potential risk in an infected patient.

Q. Ideally treatment with steroids should only be considered after having obtained histological evidence for the diagnosis. Outline the considerations relating to a biopsy in this patient.
A. Performing a renal biopsy in this critically ill, ventilated patient would be particularly difficult and hazardous primarily due to the risk of bleeding associated with the procedure and possible coagulopathy. It might require a specialist approach using transjugular biopsy and could have an inconclusive outcome. Careful consideration of the risks and benefits with the Nephrology team is necessary.

**NOTE** Do not feel compelled to initiate unproven treatments because there is no other specific therapy available. Do no further harm!

In Mrs A’s case, the risks of steroid treatment are felt to far outweigh the unproven benefits and is therefore withheld. Mrs A’s renal function deteriorates such that she requires renal replacement therapy (RRT) despite prompt discontinuation of her rifampicin.

The patient becomes very drowsy and then unresponsive with small pupils. She is treated by haemofiltration and her renal function recovers to a point that she no longer requires RRT after ten days.

**Learning Issues**
Renal replacement therapy
Haemofiltration

Q. Mrs A was receiving conventional dose morphine as an analgesic and to improve her tolerance of intubation and ventilation. Might this have contributed to her drowsiness?
A. Yes, it is probable that she developed opiate toxicity - due to the drug and its water-soluble metabolites. Unfortunately the dose of morphine was not reduced as Mrs A’s renal function deteriorated.
Q. How would you manage such opiate toxicity? Would there be a disadvantage to utilising an opiate antagonist?
A. Opiates should be discontinued. Administration of an opiate antagonist in an intubated patient may cause intolerance of the endotracheal tube and of ventilation.

Q. How will the opiate metabolites be eliminated?
A. Elimination of metabolites may be achieved by the remaining diminished native renal function or by RRT.

Learning Issues
Opiate toxicity

Mrs A gradually recovers normal consciousness over four days and is extubated a week after starting RRT.

Q. She asks you and the nephrologists if she will require RRT permanently. What do you tell her?
A. Cautious optimism is reasonable given the rapidity with which she has recovered. In the majority of cases of AKI presenting in the ICU a return of renal function to 90% of normal over the next six months is to be expected.

Learning Issues
Outcome

Q. Once it is evident that Mrs A no longer requires RRT, does she require continued detailed attention to her renal function?
A. She will require continued careful management until her creatinine has returned to near normal. Mrs A’s renal vascular autoregulation is unlikely to return to normal for some weeks after her insult; her ability to control her sodium, potassium, hydrogen ion and water balance will be impaired. This means that any cardiovascular, septic or drug insult will be tolerated less well than by the normal kidney, with the potential for precipitating further deterioration of renal function.

NOTE Remember that the kidney’s ability to maintain fine control of electrolyte and water balance will take some weeks to recover.

Mrs A recovers from her septic state and her drug-induced interstitial nephritis. She is discharged home five weeks after her emergency surgery, with a creatinine of 125 µmol/L (1.4 mg/dL). Her creatinine had returned to 80 µmol/L (0.9 mg/dL) when seen at the follow-up clinic six months later.
Patient 2

A 25-year-old man, Mr B, is admitted to the hospital unconscious. He had started working on his car with the engine running in a closed garage. He had taken the precaution of leaving only a small quantity of fuel in the tank and the engine had stopped by the time he was found several hours later.

On admission he was hypothermic (34.5 °C), heart rate 140/min, BP 80/50 mmHg with a severe metabolic acidaemia (BE −20) and carboxyhaemoglobin level of 35%. The serum creatinine was 256 µmol/L (2.9 mg/dL) and urea 9 mmol/L (25 mg/dL). There were red decubitus markings over his right shoulder, lower leg and buttock corresponding to the position in which he had been found lying on the floor.

See the PACT module on Environmental hazards.

On arrival he was intubated and ventilated with 100% oxygen and resuscitated with intravenous fluid which restored his blood pressure to 110/70 mmHg and a CVC was placed. His CVP, despite an initial increase after each fluid challenge, then repeatedly continued to fall. However, his perfusion began to improve and as it did, the urine obtained via the urinary catheter was noticed to be brown (see image below), contained obvious sediment and was strongly positive for blood on dipstick testing. Microscopy revealed no red cells in the spun sediment.

![Image of brown urine](image)

**Learning Issues**

PACT module on Airway management

Renal perfusion

Dipstick urinalysis and Microscopy of urine

PACT module on Oliguria & anuria (AKI Part I)

Q. What is the likely cause of the oliguria and renal dysfunction clinical diagnosis?

A. The decubitus markings and the history of unconsciousness and hypotension (over a long period) suggest a pressure (decubitus) injury and rhabdomyolysis.

Q. What is the pathological process underlying the urine changes and the high creatinine (relative to the urea level)?

A. The urinary changes suggest the presence of myoglobin in the urine (urinalysis positive for ‘blood’ but no red cells on microscopy). Muscle necrosis is also suggested by the relatively high creatinine.
Q. What confirmatory investigations are appropriate?
A. Serum creatine phosphokinase (CPK) is rapidly measured and, although the test may not be immediately available, urine may be tested for the presence of myoglobin. Due to muscle destruction, a serum pattern may be evident - serum potassium (and phosphate) is usually unexpectedly high and calcium is low.

Q. Should therapy await confirmation of the full rhabdomyolysis picture?
A. No. The institution of aggressive (particularly intravenous fluid) treatment should not be delayed while awaiting the results.

Q. Why is this young man requiring such large volumes of fluid to maintain his circulating volume?
A. The extent of the muscle damage is considerable and as his perfusion pressure has risen with fluid resuscitation he has begun to sequester large quantities of fluid in his damaged muscle.

The major threat to renal function in rhabdomyolysis is the severe extracellular fluid depletion combined with the toxic effects of the products of muscle breakdown.

The CPK of Mr B is found to be very high at 124,000 iu/L confirming the diagnosis of rhabdomyolysis. By this time the right buttock and shoulder have begun to swell very obviously.

Severe swelling of the buttock following pressure induced muscle necrosis

Learning Issues

Rhabdomyolysis

NOTE If you suspect rhabdomyolysis you must act quickly.
Q. What measures must be taken to prevent the development of established AKI?
A. Maintenance of the circulating volume is essential as large quantities of fluid are sequestered in the muscle.

Q. Is alkalinisation of the urine by the administration of sodium bicarbonate important?
A. Theoretically, it may reduce precipitation of the acidic by-products of blood which cause tubular damage. Although utilised in the treatment of trauma, the evidence has not warranted its inclusion in consensus statements.

The importance of alkalinisation appears to be much less than the maintenance of a high normal circulating volume by replacement of ECF volume.

Assistance from general or plastic or orthopaedic surgeons may be needed to determine if there is a compartment syndrome requiring fasciotomy or necrotic muscle that requires excision.


Volume therapy with intravenous fluid is the key to circulatory (and renal) support.

Multiprofessional collaboration

Mr B’s circulation is maintained as his muscles swell. He requires a positive fluid balance of 12 litres over the first 36 hours. It was decided to alkalinise his urine using an isotonic sodium bicarbonate infusion as part of his resuscitation fluid.

His carboxyhaemoglobin rapidly falls and his level of consciousness improves. The surgical team assesses his muscle injuries and he is taken for fasciotomy of his lower leg compartments. No muscle resection is required. His urinary output is established at greater than 100 mL/hr and his creatinine peaks at 48 hours at a level of 358 μmol/L (4 mg/dL) before returning to normal. He makes a good functional recovery.

Learning Issues
Treating complications
PACT module on Electrolytes and Homeostasis
Mr C, aged 68, is brought to the Emergency Department unconscious, hypotensive and in respiratory distress. His arterial blood gases on admission show PaO₂ 7.9 kPa (59 mmHg) (FiO₂ 1.0), PaCO₂ 5.2 kPa (39 mmHg), pH 7.01 and BE −24 mmol/L. His potassium is 9.8 mmol/L. His ECG is as shown (classic hyperkalaemia with bradycardia, absence of p wave and QRS almost a sign wave). You have been called to see him to assist and just as you arrive he vomits, aspirates and has a respiratory arrest.

Learning Issues
ECG changes of hyperkalaemia
Management of acute hyperkalaemia

Q. What are your priorities?
A. Follow the ABC of resuscitation: establish the airway and ensure adequate oxygenation and ventilation. Restore the circulation with fluid and, after CVC insertion, with vasopressors and inotropes guided by CVC monitoring (CVP and ScvO₂).

Q. His PaCO₂ of 5.2 represents an inadequate ventilatory response to the pH of 7.01. What level of ventilatory support will you initiate?
A. A high minute volume will be required to keep the pCO₂ low. Any level of inadequate respiratory compensation will exacerbate his acidaemia and will worsen his hyperkalaemia.

Q. What is the next priority?
A. Specific measures to correct his hyperkalaemia.
See the PACT module on Electrolytes and Homeostasis.

Intravenous calcium was administered in a dose of 10 mL of 10% calcium gluconate given fairly quickly as a stat intravenous dose by the Emergency Department doctor, given the hyperkalaemia is known to be a cause of cardiac arrhythmias. This dose was titrated to effect and was repeated up to a total of 30 mL.
Q. Calcium therapy does not result in a significant change in the serum potassium concentration. How does it work in this circumstance?

A. Intravenous calcium acts as a physiological antagonist to potassium.

Intravenous insulin lowers the serum potassium concentration by approximately 0.6 to 1.0 mmol/L (mEq/L) and is widely used to treat patients with hyperkalaemia. However, insulin promotes potassium uptake into the cells by mechanisms independent of glucose entry and hence glucose should also be administered to prevent hypoglycaemia. A commonly used regimen is 10 units of regular insulin as an intravenous bolus, followed by 50-100 mL 50% dextrose solution given through a peripheral line (or CVC, if available) as a rapid infusion. In some countries, such as the UK, insulin/dextrose is given simultaneously over 20-30 minutes.

Nebulised β2-agonists may be valuable when intravenous access is difficult. The usual adult dose is 10-20 mg of salbutamol by nebuliser over 10 minutes i.e. the dose of salbutamol recommended for the acute management of hyperkalaemia is 3-4 times that of the dose used for bronchodilation. The transcellular shift of potassium into the cells by salbutamol may be attenuated in patients receiving beta-blockers.

Q. Considering the above two therapies, is dual therapy worthwhile?

A. It is generally recommended that dual therapy (with both insulin/dextrose and nebulised salbutamol) be used for acute management of hyperkalaemia in critically ill patients since dual therapy reduces serum potassium more than mono therapy.

Alkalisation, with either sodium bicarbonate or hyperventilation, to drive potassium into the cells can rapidly reverse the adverse physiological effects of hyperkalaemia. This approach is not recommended as the first line of therapy in patients with hyperkalaemia but in this case where the patient is concurrently acidaemic, it is reasonable to use it.

Cationic-exchange resins can be given orally or as an enema to sustain lower serum potassium levels, once some or all of the above measures have been initiated, provided the GI tract is available.

NOTE: Ensure adequate oxygenation and hyperventilation in the presence of a severe metabolic acidaemia.

Learning Issues
Treatment of hyperkalaemia

As his resuscitation is proceeding more history is obtained. Mr C has been having nocturia 3-4 times per night and is due to see the urologist. He has been taking diclofenac for bone pain for the last three months. This has been thought to be due to an osteoid osteoma, which was to be dealt with by the orthopaedic surgical service next month. Just then his urea is reported to be 96 mmol/L (269 mg/dL) and his creatinine 1783 µmol/L (20 mg/dL). Blood sugar is normal. Blood lactate is 2.5 mmol/L (22.5 mg/dL).
Q. What other features of the physical examination might you concentrate upon in view of this information?
A. The abdomen including a rectal examination.

The examination of his abdomen revealed a smooth round mass emerging from the pelvis (likely to be a distended bladder) and a rectal exam revealed a hugely enlarged smooth prostate.

Learning Issues
Lower urinary tract patency

Q. What procedure will you do next?
A. Catheterisation of the bladder.

Q. If it is not successful per urethra, what is a reasonable next step?
A. The patient may require the insertion of a suprapubic catheter.

Q. Obstructive uropathy is likely the primary pathology here. What is its mechanism of action?
A. Obstructive uropathy would produce distal tubular damage and then renal failure as the pressure in the lower urinary tract increases. Superinfection of the obstructed urinary tract may exacerbate.

Q. The recent taking of NSAIDs would further accentuate the hyperkalaemia. Outline its mechanism of toxicity.
A. Nephrotoxicity may be mediated by its distal tubular effects; also by causing glomerular malfunction and interstitial damage.

Learning Issues
Obstructive uropathy
Actions of common nephrotoxic drugs

Mr C is catheterised successfully and 1800 mL of urine is obtained. By this time he is being ventilated (MV 15 L/min) with adequate oxygenation on a high FiO₂. His circulation has improved after the administration of three litres of fluid, partial correction of his hyperkalaemia to 6.6 mmol/L and support from dobutamine and norepinephrine by infusion through his CVC. Broad-spectrum antibiotics have been given after blood and urine were cultured. Urinary output is 150 mL in the past hour. He is transferred to the ICU.
Q. In managing his renal failure, would you institute immediate RRT or wait to allow an assessment of the other therapies to date?

A. It would be reasonable to either use RRT immediately or wait and see if relief of the obstruction will allow recovery of some renal function. Rapid correction of his uraemia by RRT, particularly intermittent haemodialysis, would risk severe disequilibrium syndrome and this would therefore be better done gradually.

Q. Given that in this case the acidaemia seems to be secondary to his renal failure and that he is now passing urine, does this influence your choice?

A. Yes, it allows more leeway in correcting the metabolic acidaemia with isotonic sodium bicarbonate and this will also help to control hyperkalaemia.

Measuring the serum and urinary sodium concentrations, in conjunction with the information from the CVC, will allow the appropriate volumes and proportion of sodium and free water to be administered as the post-obstructive osmotic diuresis ensues. Regular measurement of his serum creatinine and urea will allow an assessment of the likely speed of recovery of his biochemistry allowing a more leisurely decision on whether to institute RRT.

**Learning Issues**

Indications for instituting renal replacement therapy
Correction of metabolic acidaemia

**NOTE** Correct the metabolic acidaemia gradually. In obstructive uropathy, the kidney cannot eliminate non-volatile hydrogen ions.

Mr C increases his urine volume over the next two hours to 350 mL/hr and his urea and creatinine begin to fall. He requires a positive balance of six litres over the next 48 hours and his urea and creatinine steadily fall. His acidaemia is corrected over the next 48 hours. E. coli is grown from his urine and blood. He steadily improves and his respiratory failure corrects over the next 15 days. He is eventually discharged from hospital with an indwelling catheter, to return for prostatic resection once he has recovered his muscle mass. Investigation of his lower urinary tract showed dilation of the ureters and hydronephrosis. His creatinine has stabilised at 215 µmol/L (2.43 mg/dL) and urea at 12 mmol/L (34 mg/dL).

Q. What do you think the likelihood is that Mr C’s renal function will return to normal with time?

A. It is unlikely that Mr C’s renal function will return to normal given the degree and duration of time of the obstruction when he presented. The well-established hydronephrosis still present at discharge supports the length of time that his obstruction had been present.

Mr C’s creatinine never fell below 210 mmol/L (2.38 mg/dL) over the next three years.
On reflection, you have been presented with three challenging cases of critically ill patients with AKI. In each patient the cause was a pathological process outside the kidney, rather than primary renal disease (as is usually the case in clinical practice). These cases emphasise that the aetiology of AKI in critically ill patients is frequently multifactorial, that the cause may not be immediately obvious, that treatment decisions may be complex and that collaboration with a nephrologist is therefore essential.

Q. Thinking about the management of these three patients, what are the key messages you have learned about how best to preserve or restore renal function?

A. The key messages are:

- Restore the circulating volume and renal perfusion pressure.
- Careful clinical examination and specific investigations required to establish the diagnosis in individual cases.
- Institute effective treatment for the primary disease process.
- Avoid nephrotoxic drugs.