DCCQ

Renal Group

The Renal Handbook

Academic Department of Critical Care
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This renal handbook is designed for use on the Queen Alexandra Hospital Intensive Care Unit. It is not a comprehensive renal textbook but aims to provide some practical guidance at the bedside for all members of staff. This version has been fully updated and takes into consideration current thinking within the field of Critical Care Nephrology. Full and up to date renal guidelines are available via the Intranet site.

For use outside of the Department of Critical Care: Any guidelines or recommendations within this handbook have been prepared carefully and in good faith for use within the Department of Critical Care at Queen Alexandra Hospital. No liability can be accepted by Portsmouth Hospitals NHS Trust for any errors, costs or losses arising from the use of any guidelines or information contained herein.

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Abbreviations

ICU	Intensive Care Unit
AKI	Acute kidney injury
GFR	Glomerular filtration rate
eGFR	Estimated GFR
CKD	Chronic kidney disease
DCCQ	Department of Critical Care, Queen Alexandra Hospital, Portsmouth
RBF	Renal blood flow
ADH	Anti diuretic hormone
ATN	Acute tubular necrosis
CI-AKI	Contrast induced AKI
NAC	N-acetyl cysteine
RRT	Renal replacement therapy
CRRT	Continuous renal replacement therapy
IHD	Intermittent haemodialysis
CVVH	Continuous veno venous haemofiltration
CVVHD	Continuous veno venous haemodialysis
CVVHDF	Continuous veno venous haemodiafiltration
SCUF	Slow continuous ultrafiltration
PD	Peritoneal dialysis
HD	Haemodialysis (generally taken to mean IHD)
RTx	Renal transplant

Acute kidney injury

Definition and grading of acute kidney injury

Acute failure of normal renal function is an abrupt (less than 7 days) and sustained decrease in kidney function, accompanied by a rise in creatinine and urea, a fall in urine output or both. By this definition, acute renal failure could be anything from a transient rise in creatinine that gets better over a couple of days, to the need for renal replacement therapy. Taking this into consideration the term acute kidney injury (AKI) rather than acute renal failure is now used.

For years there has been no standard way of defining AKI, various definitions use biochemical markers (urea and creatinine), glomerular filtration rate or urine output.

Biochemical markers: Urea and creatinine rise but they are often quite insensitive markers. For example, serum creatinine is affected by non-renal factors such as age, sex, race and muscle bulk. The glomerular filtration rate (GFR) has generally fallen by about 50% before the serum creatinine starts to rise so there is a lag time between injury and seeing the creatinine start to rise.

Glomerular filtration rate: Changes in creatinine and urine output are surrogates for changes in GFR. However formal, accurate measurement of GFR is not practical at the bedside on ICU so there are a number of creatinine based estimations of GFR available (eGFR). These include the MDRD formula and the Cockcroft and Gault formula. Although these are useful in some situations, their individual limitations need to be remembered (e.g. whether they adjust for body weight, the population demographic from which they were first derived and validated in) but importantly it should be remembered that they use creatinine for their calculations (see above for limitations of creatinine) and the GFR during AKI is very dynamic.

Urine output: Changes in urine output can be used to define renal failure, but this is confounded by the use of diuretics and not all cases of renal failure are associated with oliguria. It should be remembered that damaged renal tubules are unable to concentrate urine so 'water' rather than 'good quality urine' will be passed and may be falsely reassuring.

Future work: There is much interest in kidney biomarkers – something that will not only give an indication of function but also indicates when injury has occurred – and when recovery is happening. Potential biomarkers indicating renal injury include kidney injury molecule-1 (KIMI-1), neutrophil gelatinase associated lipocalin (NGAL), interleukin 18 and urine cystatin C. There are many interesting reviews in the literature, but biomarkers are not currently used in day to day practice.

Definition of AKI

The 'Kidney disease: Improving global outcomes' (KDIGO) **definition** of AKI (generally well accepted) is any of the following:

- An increase in serum creatinine by ≥ 26.5 µmol/l within 48 hours
- An increase in serum creatinine by ≥1.5 times baseline which is known or presumed to have occurred within the past 7 days
- Urine volume ≤ 0.5 ml/kg/hour for 6 hours

Grading of AKI

In an effort to standardise how we **grade** the severity of kidney injury, classification systems were developed, initially the RIFLE system and then the AKIN system and more recently the KDIGO classification.

RIFLE (table 1) is an acronym for 3 levels of renal dysfunction (risk, injury and failure) and 2 possible outcomes (loss of kidney function or end stage kidney disease). It has been validated in a large number of patients with different conditions and has been shown to correlate with outcome. The presence of 'risk' at least doubles your hospital mortality and 'failure' can lead to an up to 10 fold increase in mortality.

Table 1: The RIFLE classification of acute kidney injury *(ADQI group, Critical Care 2004)*

		Creatinine	GFR	Urine output
R	Risk of renal dysfunction	Increased 1.5 fold	Fall > 25%	Less than 0.5ml/kg/hr for 6 hrs
I	Injury to kidney	Doubled	Fall > 50%	Less than 0.5ml/kg/hr for 12 hrs
F	Failure of kidney function	Increased 3 fold OR acute rise of > 44µmol/l so that creatinine now > 350 µmol/l	Fall > 75%	<0.3ml/kg/hr for 24 hours or anuria for 12 hours
L	Loss of kidney function	Complete loss of kidney function for more than 4 weeks		
E	End stage renal disease	The need for dialysis for longer than 3 months		

** AKI should be both abrupt (within 1-7 days) and sustained (> 24 hours)*
ADQI: Acute dialysis quality initiative group

AKIN (table 2) is a classification devised by the Acute Kidney Injury Network and is similar to the RIFLE system but does not include any outcome grades and was modified to take into the account that even small changes in creatinine (> 26.5µmol/l within a 48 hour period) are significant. These modified criteria have again been validated in large patient groups with similar findings to RIFLE. However for both RIFLE and AKIN there were some limitations. The criteria were not always being applied consistently, it was unclear what to do with patients who already had an elevated creatinine on admission, and then there are all the limitations that go with using creatinine and urine output.

Table 2: The AKIN classification *(AKIN Critical Care 2007)*

	Creatinine	Urine output
I	Increase of ≥ 26.5 µmol/l * OR increased 1.5-2 fold from baseline**	Less than 0.5ml/kg/hr for more than 6 hours
II	Increased >2 to 3 fold from baseline	Less than 0.5ml/kg/hr for more than 12 hrs
III	Increased > 3 fold from baseline OR ≥ 354 µmol/l with an acute increase of at least 44umol/l OR need for renal replacement therapy	<0.3ml/kg/hr for 24 hours or more OR anuria for 12 hours or more

** within 48 hours*
*** within the prior 7 days*

The most recent published classification is the KDIGO system (table 3) which is a combination of RIFLE and AKIN criteria. When RIFLE and AKIN had been compared, there were patients that one system identified and the other didn't, hence the rationale of combining the 2 systems.

Table 3: KDIGO staging of AKI *(Kidney International 2012)*

	Creatinine	Urine output
I	Increase of ≥ 26.5umol/l OR 1.5-1.9 times baseline	Less than 0.5ml/kg/hr for 6-12 hours
II	2-2.9 times baseline	< 0.5ml/kg/hr for ≥12 hrs
III	3 times baseline OR increase to ≥ 354 µmol/l OR need for renal replacement therapy	<0.3ml/kg/hr for ≥ 24 hours OR anuria for ≥12 hours

** Patients should be staged according to the criteria that give them the highest stage (e.g. creat or UOP)*
** Within 48 hours*

All staging systems rely on knowing the baseline creatinine. If it is not known it can be estimated (e.g. using MDRD formula) but there is still the unknown as to whether they may have CKD.

Incidence and outcome

Using 'standard' definitions, AKI develops in 5-7% of hospitalised patients with up to 60% of patients on the ICU developing AKI. However given the variation in definition, these numbers may not tell the whole story.

Some patient groups are more likely to develop AKI, but for any condition, developing AKI (by whatever definition) is associated with an increased mortality which rises further if renal replacement therapy is needed (table 4). There is something about developing renal failure that increases your risk of death. It is not clear whether this is related to the systemic effects of renal failure itself, the effects of its treatment or is simply a reflection of the severity of the underlying condition. Whatever the cause, prevention of AKI is the key.

Table 4: Effect of acute kidney injury (AKI) and renal replacement therapy (RRT) on mortality

	Incidence AKI	Mortality – no AKI	Mortality with AKI	Mortality with AKI +RRT
Hospital	5-7%		5-20%	
ICU	1-25%		23-80%	57-80%
Severe sepsis	19-51%	45%	70%	
Post angiography	3%	4%	12%	
Post CABG	8%	1%	5-20%	60%

It has been shown very nicely that there is no such thing as 'just a little bit of renal failure'. Even what we used to consider possibly a non-significant rise in creatinine has been shown to have an adverse effect on mortality.

Rise in creatinine	Multivariate OR Hospital mortality	Increase in LOS
≥ 26.4 µmol/l	4.1	
≥ 45 µmol/l	6.5	3.5 days
≥ 90 µmol/l	9.7	5.8 days
≥ 180 µmol/l	16.4	7.9 days

Chertow 2005 JASN (OR = odds ratio, LOS = length of stay)

The Financial burden of AKI

It has been calculated that the cost of AKI to the NHS in England in 2009-10 was somewhere between £434-£620 million pounds *[Health Services Journal, June 2011].* This includes the cost of acute admission, the cost to critical care (£141-£217million) and the cost for those needing ongoing renal replacement therapy. If up to 30% of AKI is preventable, then this could save the NHS £130-186 million/year. The total cost of AKI to the NHS is estimated to be more than lung cancer and skin cancer. Put like that you realise how important an issue AKI is.

Causes of acute kidney injury

So why do kidneys go bad? From a pathophysiological point of view the kidneys are either not perfused, they are unable to filter fluid at the glomerulus due to damage to the glomeruli (e.g. glomerulonephritis), there is failure of the tubules to allow free passage of the ultrafiltrate out due to damage to the tubules (e.g. toxic damage) or a combination of these factors. If there is a failure of filtration this is seen as a fall in the glomerular filtration rate.

The causes of AKI are classically divided into pre renal, intrinsic and obstructive causes.

Pre renal failure (Figure 1)

The kidneys are very good at maintaining a constant blood flow (renal blood flow, RBF) over a wide range of mean arterial pressure. They regulate pressure within the afferent and efferent arterioles (a process called autoregulation) and maintain perfusion by triggering protective processes involving anti diuretic hormone (ADH) the renin-angiotensin-aldosterone system and the sympathetic nervous system. All of this aims to preserve blood flow to the kidney, increase the fraction of plasma filtered and increase the amount of fluid reabsorbed by the kidney. How well the kidney can do all of this depends on a number of factors: for example any underlying renal/vascular disease and the presence of certain drugs that may interfere with this compensatory mechanism. 'Pre renal failure' is an extension of the body's physiological response when compensatory mechanisms are overwhelmed and perfusion to the kidney is compromised.

If perfusion is returned to normal the kidneys return fairly promptly to their baseline. If however perfusion is compromised for a significant period of time, further damage to the kidneys can occur. In a few cases this damage may be irreversible.

For the kidneys (and indeed any organ) to be perfused and therefore function they need:

- ***Pressure***: Hypotension which may be absolute or relative to the patient's *normal* blood pressure. This may be due to loss of volume or due to vasodilatation (e.g. drugs, loss of vascular tone, sepsis).

- ***Volume***: The volume may be lost (e.g. haemorrhage, diarrhoea, vomiting) or redistributed and in the 'wrong place' (e.g. pancreatitis, ascites, nephrotic syndrome).

- ***Flow***: This refers to cardiac output. Despite an acceptable blood pressure, if the cardiac output is low then the kidneys will not be perfused adequately.

- ***No obstruction***. There must be patent vessels and a way out for the urine.

Intrinsic renal failure (Figure 2)

The commonest cause of intrinsic renal failure on the ICU is ischaemic acute tubular necrosis (ATN). This accounts for up to 80% of cases of AKI on the ICU. It develops following profound or prolonged pre renal failure and is suggested by the persistence of renal failure despite restoring pressure, flow and volume to the kidneys. Technically ATN is a histopathological diagnosis but over time has become a clinical diagnosis however the question should always be asked, *why* has it developed (what is the cause) rather than just assigning the label of 'ATN'. ATN can also develop secondary to a variety of intrinsic (e.g. myoglobin in rhabdomyolysis) or extrinsic renal toxins (e.g. poisons, drugs).

Following the initial insult to the kidneys, the primary response is constriction of the glomerular arterioles in response to vasoconstrictors such as endothelin, antithrombin III, thromboxane A_2, leukotrienes and the sympathetic nervous system. There is also a failure of compensatory vasodilatation in response to nitric oxide and prostaglandin E_2. Ultimately damage to the tubules occurs with loss of the normal tight junctions between the tubular cells allowing paracellular leakage. Sloughing of tubular cells into the tubular lumen, together with precipitation with proteins can lead to 'micro-obstruction'. This is the initiation phase of ATN. Following this there is a maintenance period with oliguria and a GFR that may be < 10mls/min. Dialysis may be needed but some kidneys may open up, however this may take up to 6 weeks – remembering this is from the time of the last kidney insult, multiple episodes of hypotension and nephrotoxic drugs may delay this. Hopefully this is then followed by a period of recovery, where there is repair and regeneration of renal parenchymal cells. Until the tubules remember how to concentrate urine, any urine that is passed may not be good quality urine, even if the volumes are pleasing.

Vascular causes of renal failure may be present at a pre or intra renal level, and should be considered in vasculopaths, those having had vascular surgery and those having had angiography.

Despite our obsession with the different types of glomerulonephritis while at medical school, glomerulonephritis causing new AKI on the ICU is rarely seen, however it may manifest as part of a systemic vasculitis requiring critical care admission (see following).
The final compartment of the kidney is the interstitium (packing tissue), and damage to the interstitium (interstitial nephritis) can cause renal failure. There is a long list of causes of interstitial nephritis but the commonest causes on the ICU are drugs or toxins. Its diagnosis should be made by a nephrologist.

Figure 1: Causes of pre renal failure

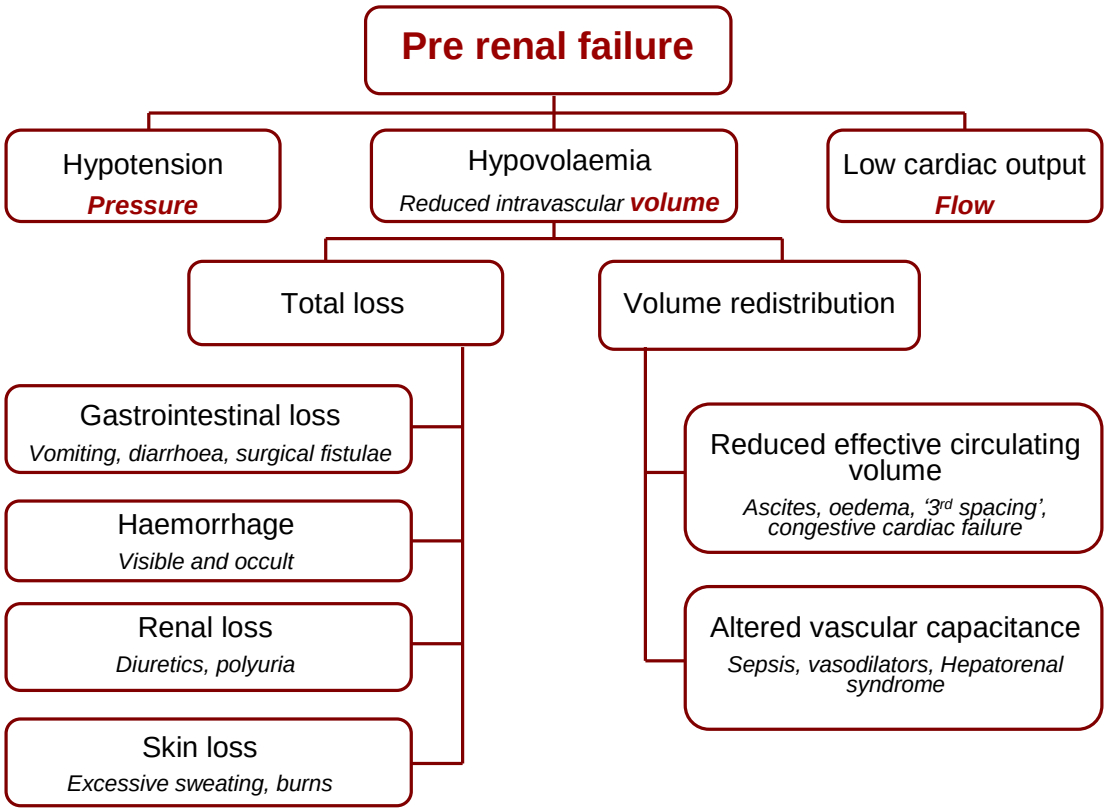
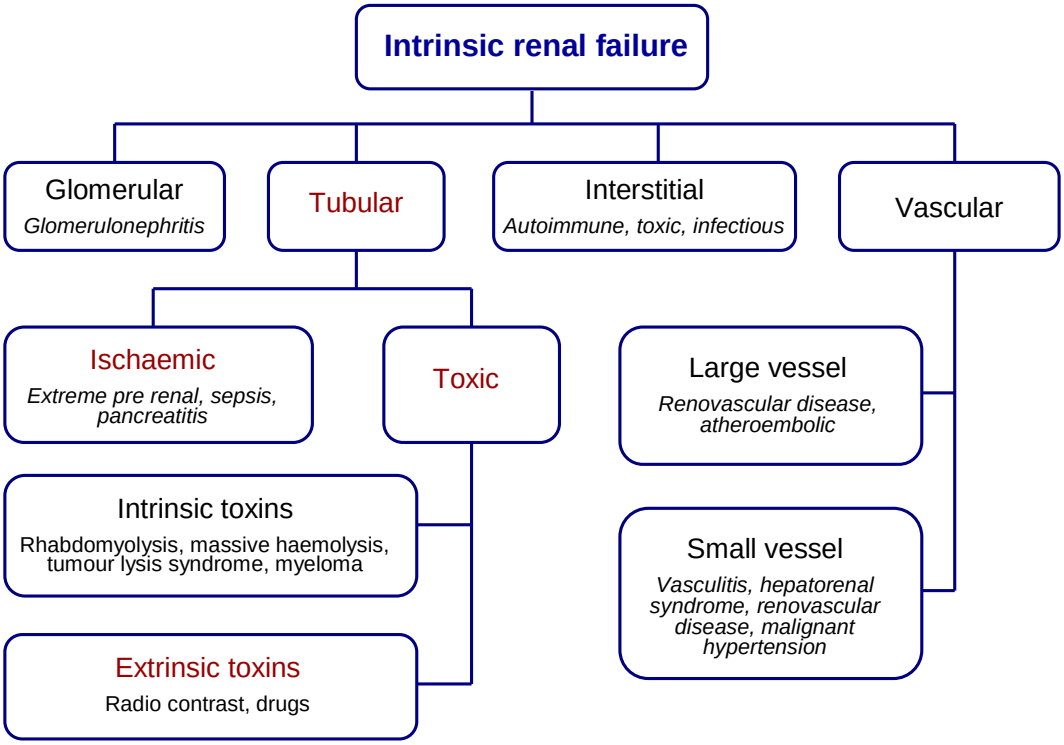


Figure 2: Causes of intrinsic renal failure ***(Red = most common causes on the ICU)***

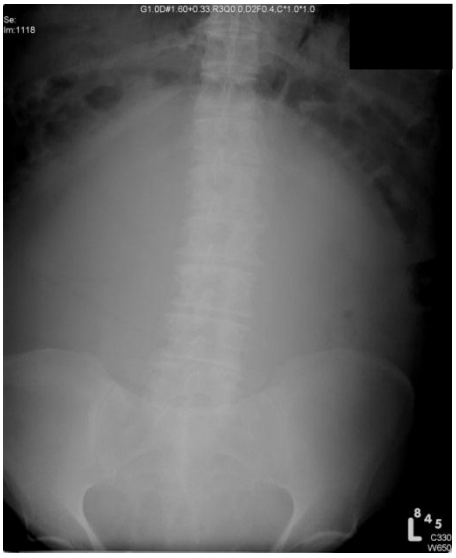


Post renal or obstructive renal failure (Figure 3)

Obstruction can occur at any level of the urinary collecting system and can be due to intrinsic (e.g. stones, tumour) or extrinsic causes (e.g. surrounding or infiltrating tumour, large inflammatory abdominal aortic aneurysms). It is an infrequent cause of AKI on the ICU but is important to be excluded in all cases. It is a simple job to flush the urinary catheter and can be very rewarding if it was blocked. Remember, the patient may still pass urine if the obstruction is not bilateral or is only partial. An ultrasound scan is the best way to rule out obstructed kidneys.

Sudden onset of absolute anuria is due to obstruction or a catastrophic vascular event until proven otherwise.

Figure 3: Abdominal X ray done for abdominal distension.



The distension was caused by a bladder full of urine – the patient was still passing urine at the time

Complications of AKI

AKI is a true multi system condition and therefore any system can be affected.

- *Retention of uraemic toxins.* Accumulation of toxins (e.g. urea) can lead to nausea, vomiting, drowsiness, a bleeding tendency and uraemic flap. Coma (uraemic encephalopathy) and a pericardial rub are less commonly seen. Uraemic frost can be seen in a text book. Many of these complications are difficult to spot on sedated ventilated patients but there are very few ICU patients who would be allowed to develop solute levels high enough to cause these symptoms.

- *Volume overload.* Salt and water retention occurs early, and is a common reason for initiating renal replacement therapy on the ICU. Volume overload is not good for oxygenation but also the development of peripheral oedema affects wound healing and pressure areas.

- *Acidosis.* There is retention of organic anions (e.g. phosphate) and reduced production of bicarbonate by the failing renal tubules. In critically ill patients this may be aggravated by the presence of a non-renal acidosis, for example lactic acidosis from sepsis and respiratory acidosis from respiratory failure.

- *Electrolyte and mineral disturbances.* Hyponatraemia, hyperkalaemia and hyperphosphataemia.

- *Anaemia.* Anaemia can develop due to inappropriate levels of erythropoietin (decreased synthesis) or increased red cell fragility causing premature red cell destruction. Uraemia is also associated with platelet dysfunction and increased risk of gastrointestinal bleeding.

- *Immunosuppression.* Renal failure itself can impair humoral and cellular immunity, putting the patient at risk of infectious complications.

- *Metabolic consequences.* Hyperglycaemia occurs due to peripheral insulin resistance and increased hepatic gluconeogenesis. Protein catabolism is also activated.

- *Drug accumulation.* Renal failure may be secondary to drugs, but as glomerular filtration rate falls renal clearance of drugs and their metabolites also falls. Renal failure may be exacerbated by drug accumulation or other side effects can develop, for example respiratory depression and drowsiness secondary to morphine metabolites.

Investigation of the cause of acute kidney injury (figure 4)

- *History history history….* Most of the time on the ICU it is obvious why a patient is in renal failure, for example they may have severe sepsis, rhabdomyolysis or had their renal arteries clamped during their emergency AAA repair. However if the cause of the renal failure is not immediately apparent a full history should be taken; from the patient, the family and the old notes where ever possible. Risk factors such as diabetes, ischaemic heart disease, peripheral vascular disease, hypertension and liver disease should be looked for.

- *Review of charts*. This should include the observation and anaesthetic charts looking for periods of profound or prolonged hypotension *in relation to the patient's usual blood pressure.* The fluid balance charts should be reviewed considering hidden losses such as sweating or 'third spacing'. The trend is important. The sudden onset of anuria suggests obstruction or a catastrophic vascular event. Remember diuretics can make the urine output look artificially good. Finally look at the drug charts, remembering drugs that may not be on the chart such as radiocontrast and drugs that the patient may have been taking before they came in, including herbal remedies.

- *Review of laboratory tests*. Determine the baseline creatinine and the pattern of change (i.e. sudden jump versus gradual decline). The rate of change may be more important than the absolute value. A urea elevated out of proportion to the creatinine may be a sign of intravascular volume depletion or may indicate an upper gastrointestinal bleed. The history

may give clues as to other tests that need to be done, for example with a history of trauma check the creatinine kinase (CK) level to exclude rhabdomyolysis.

- *Examination*. A full examination should be performed with reference to the basics:
  - *Pressure*: Mean arterial pressure *in relation to the patients usual readings*
  - *Volume*: Overall volume status as well as intravascular volume status
  - *Flow*: Cardiac output studies and/or markers of end organ perfusion (e.g. lactate). Remember raised intra abdominal pressure may reduce flow to the kidneys and an intravesical pressure may be helpful.
  - *Exclude obstruction*: Remember to make sure there is a way out for urine. Ensure that they do not have a palpable bladder and have a patent urinary catheter.
  - *Extra renal signs*: Look for the presence of rashes, joint involvement, pulmonary haemorrhage, tense limbs, evidence of liver disease etc.

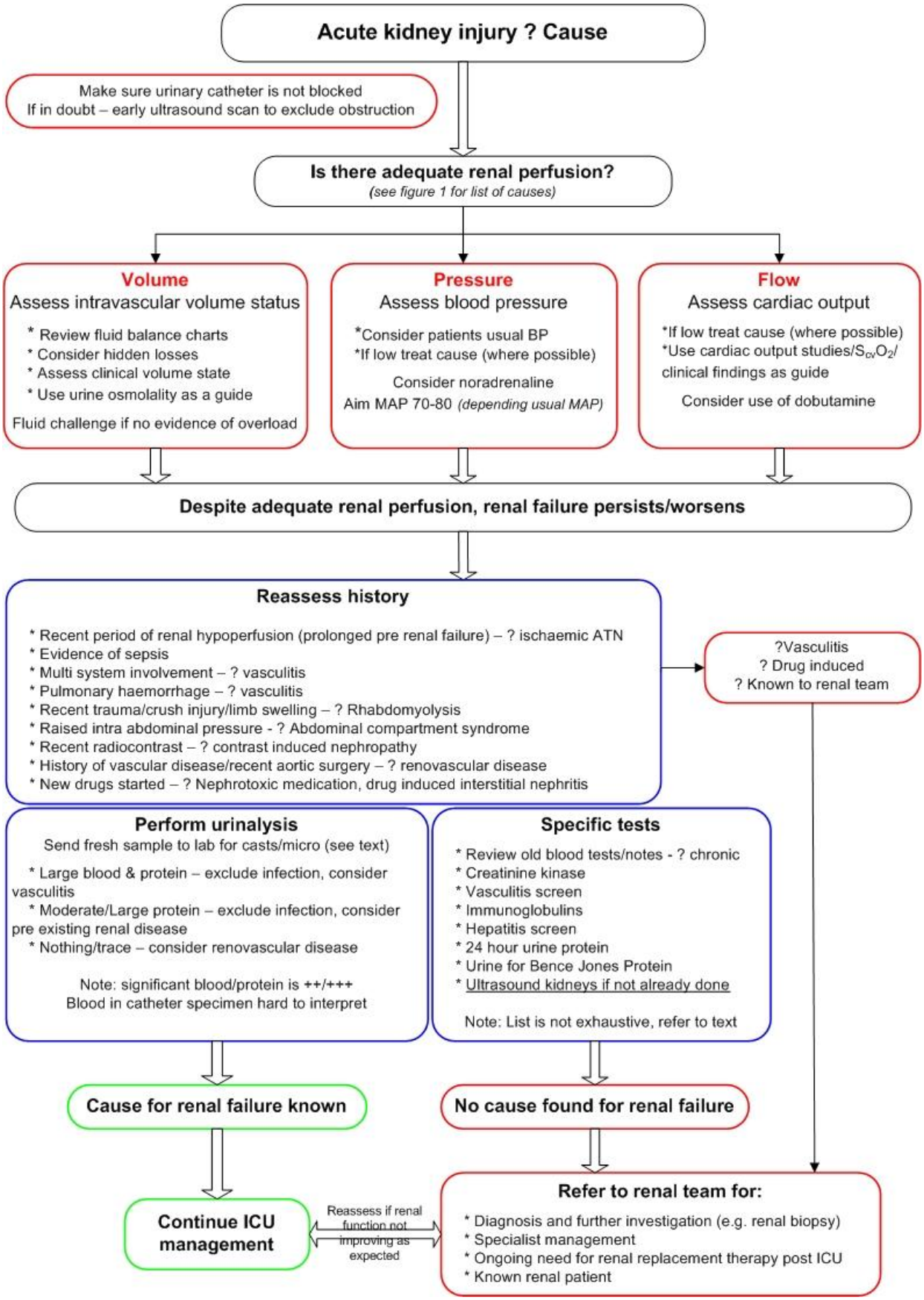
- *Urinalysis.* A standard dipstick for blood and protein should be performed and a *fresh* sample sent to look for casts and exclude infection. Urine osmolality and urinary electrolytes can be used to help distinguish pre renal failure from intrinsic kidney disease (table 5) and can act as another tool in the assessment of intravascular volume status. If a large amount of protein is detected then perform a 24 hour collection.

- *Radiological investigations.* A chest x ray will help assess volume status, but patchy infiltrates may also represent pulmonary haemorrhage as seen in certain forms of vasculitis. A renal ultrasound scan should be performed; the timing will depend on the likely cause of renal failure and the patient's clinical state. An ultrasound scan will confirm that the kidneys are non obstructed, will indicate their size (small kidneys suggests chronic disease) and may give other clues as to the cause of the renal failure.

- *Specialised investigations.* In most cases on the ICU the cause of the renal failure is generally apparent after all the above investigations. If however the cause of renal failure is still unknown, further investigations are warranted. At this stage involvement of the renal team may be appropriate as the patient may need a renal biopsy. Some of the more specialised 'renal tests' include:

  - *Vasculitis screen:* P and C ANCA, complement levels, anti glomerular basement membrane antibody and anti nuclear antibody (refer to the PHT Pathology Handbook for a good over view of available renal immunological tests). Note if a vasculitis is suspected, phone the lab (Immunology Department) when you send the sample and explain the clinical situation, they are very good at prioritising tests once they have more clinical details and know that it is urgent.
  - *Immunoglobulins and urine for Bence-Jones proteinuria*. A screen for myeloma and light chain nephropathy.
  - *Hepatitis serology.* As a screen for the cause of the renal disease and in case the patient is ultimately transferred to the renal unit.
  - *Note:* tests should not be fired off randomly – think about the possible clinical causes first!

Figure 4: Check list for causes of AKI



Interpretation of urine osmolality and biochemistry

Urinary sodium and osmolality have historically been used to help distinguish between 'pre renal failure' and 'ATN' and can be used as a guide to aid fluid therapy (Table 5). Urinary biochemistry and osmolality can be helpful when *interpreted in context with the patient's condition as a whole and taking into consideration normal renal physiology.*

Table 5: Urinary findings in pre renal failure and acute tubular necrosis

	Pre renal	Intrinsic (ATN)
Urine sodium	< 20 mmol/l	> 40 mmol/l
Urine : plasma urea ratio	> 20	< 10
Urine : plasma creatinine ratio	> 40	< 10-20
Urine : plasma osmolality	> 1.5	< 1.1-1.2
Urine osmolality	> 500	< 300-500
Fractional excretion of Na [1]	< 1%	> 1%

[1] Fractional excretion of sodium (FE_{Na}): In a pre renal state sodium is actively reabsorbed by working tubules in order to maintain intravascular volume. The kidney will therefore produce concentrated urine with a low concentration of sodium. Creatinine is still excreted but relatively less sodium appears in the urine. Hence, if the tubules are intact, less sodium will be excreted compared to creatinine (*fractional excretion*).

$$\text{FE Na} = \frac{\text{Urine Na} \times \text{plasma creatinine}}{\text{Plasma Na} \times \text{Urine creatinine}} \times 100$$

Put simply: in the face of intravascular volume depletion kidneys retain water and sodium. Water is retained through the release of anti-diuretic hormone (ADH); the renal tubules hold onto more water therefore a smaller volume of more concentrated urine is produced. Sodium retention is increased through stimulation of the renin-angiotensin-aldosterone system; the renal tubules hold onto more sodium so less is excreted in the urine. Therefore, in the setting of intravascular volume depletion the kidney will produce concentrated urine (high osmolality > 500 mosmol/kg) with a low sodium content (< 10-20 mmol/l) – *if* the tubules are working properly. If the tubules have been damaged (e.g. ATN), they will not be able to adequately perform these functions and urine osmolality will be low (<300-500 mosmol/kg) and sodium high (>40 mmol/l).

There are however certain situations where patients don't fall into the commonly used classification and caution should be used.

For example:

1. *Normal physiology*. Although ADH release is triggered by changes in plasma osmolality and intravascular volume status, there are non-osmotic stimuli for release such as pain, stress and nausea. Even an adequately filled patient will attempt to retain more water and sodium in times of stress and therefore will produce low sodium, concentrated urine.

2. *Real life*. Critically ill patients on the ICU rarely have just one problem, this also goes for physiology; there is seldom just one disturbance. Although we categorise renal failure neatly into 'pre' and 'intrinsic' their pathophysiology (and therefore urinary abnormalities) is rarely this neatly defined and a degree of overlap occurs.
3. *Frusemide*. Any urinary biochemistry and osmolality needs to be interpreted with extreme caution if frusemide has been given.
4. *Chronic renal failure*. Some patients may have a salt wasting condition and the urinary sodium will be high even when they are well. Acute on chronic renal failure may make urinary findings hard to interpret.

A quick guide to urinary sodium and osmolality:

- *Urine Na < 20-30 suggests kidneys retaining Na appropriately*
- *Urine osmolality > 500 suggests kidneys concentrating urine appropriately*
- *If tubules work – should be 20 times as much urea in urine*
- *If tubules work – urine osmolality should be at least twice plasma osmolality (if urine osmolality and plasma osmolality similar – tubules not working)*

To biopsy or not to biopsy

Sometimes from the history and investigations the cause of the renal failure is still not known and specialist input may be needed. Certainly if there is any situation where an acute vasculitis is suspected, the renal team should be involved sooner rather than later as a renal biopsy may be important to their diagnosis and subsequent management.

Performing a renal biopsy on a ventilated, unwell ICU patient is not easy – although not impossible. Possible situations when a renal biopsy may be indicated are:

1. Possible systemic vasculitis
2. Multisystem disorder of unknown aetiology where a tissue diagnosis is needed
3. AKI of unknown cause
4. Biopsy of renal transplant to confirm rejection or other cause of renal failure

The number of renal biopsies done on the ICU is very small – especially when one considers the number of patients who develop some form of renal failure.

Management of the patient with an acute kidney injury

This falls into 5 areas:

1. Risk assessment - prevention is better than treatment
2. Recognise the presence of AKI and identify the cause
3. Continue to optimise renal perfusion and manage the medical complications of AKI
4. Assess the need for renal replacement therapy with timely initiation if needed (see later)
5. Continue to optimise renal perfusion, manage the medical complications and avoid further renal insults while the patient is recovering from an episode of AKI

1. Risk assessment

There are certain factors/conditions that put patients at increased risk of developing AKI. These include advanced age, co-morbidities (such as diabetes, heart failure), medications (such as ACEI, diuretics, NSAIDS), hypovolaemia, sepsis and CKD. In the 2009 NCEPOD report (AKI: adding insult to injury) it was found that 29% of patients did not have adequate assessment or documentation of the most important risk factors for AKI. The commonest areas of omission were medication, co-morbidity and hypovolaemia. In 2013 NICE published very comprehensive guidelines on 'Acute Kidney Injury: Prevention, detection and management up to the point of renal replacement therapy'. In this guideline the following risk factors are particularly applicable to ICU patients (table 6):

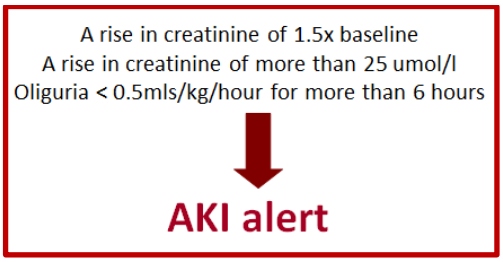
Table 6: NICE recommendations 2013 for risk assessment of AKI

Identifying AKI in adult patients with acute illness	Assessing risk factors in adults having surgery
CKD (eGFR < 60ml/min/1.73m^2 at particular risk)	CKD (eGFR < 60ml/min/1.73m^2 at particular risk)
Heart failure* Circulatory failure#	Heart failure*
Liver failure	Liver disease
Diabetes	Diabetes
History of AKI	Emergency surgery (esp when septic or hypovolaemic)
Oliguria (< 0.5mls/kg/hour)	Intraperitoneal surgery Cardiac surgery especially with prolonged CPB#
Age > 65 years	Age > 65 years
Use of nephrotoxic drugs (including contrast)#	Use of nephrotoxic drugs in perioperative period
Hypovolaemia (including those at risk of dehydration)	
Sepsis, circulatory shock#	
Deteriorating early warning scores	
History suggestive of urinary tract obstruction	
Trauma#	

** This includes chronic heart failure and acute heart failure*

#Not listed in NICE report but should be considered as part of risk assessment

At the stage of recognising that the patient is at risk of developing AKI, risk factors should be addressed where possible. For example: stop all nephrotoxic drugs, address pressure/volume/flow (see below) and consider appropriate level of monitoring (including monitoring biochemistry and urine output)



Importantly recognise the presence of AKI and try to identify the cause. You cannot treat AKI unless you recognise it in the first place. The 2009 NCEPOD report found that there was an unacceptable delay in the recognition of AKI in 12% of cases.

It is always important to know *why* the patient has renal failure as there are certain causes of AKI that need specific treatments. For example:

- *Rhabdomyolysis*: Early and aggressive hydration, urinary alkalinisation and fasciotomies if there is evidence of ongoing compartment syndrome.
- *Abdominal compartment syndrome*: An elevated intra abdominal pressure (IAP) reduces venous return and the high venous pressures in the thorax are transmitted down to the renal veins leading to end organ oedema. Decreased venous return also leads to reduced cardiac function and hypotension so arterial supply to the kidneys is also compromised. All this is made worse by extrinsic retroperitoneal compression due to the increased intra abdominal pressure. Renal compromise starts to occur when the IAP is over 20-24 mmHg (normal IAP < 7 mmHg). Treatment will depend on the cause (e.g. open the abdomen, drain ascites.)
- *Acute vasculitis*: This will need immunosuppressive drugs and/or plasma exchange (see later).
- *Malignant hypertension*: This will need aggressive treatment of blood pressure.
- *Drug induced interstitial nephritis*: Stop the offending drug and consider steroids.
- *Obstructive uropathy*: Catheterisation for a lower tract obstruction but nephrostomies may be needed for ureteric obstruction.

2. Optimise renal perfusion

- Apply the 'Three Bears Principle' of fluid balance – not too much, not too little, just enough! Ensure that the patient is well hydrated but avoid giving excess fluid – especially if it is apparent that the patient is no longer fluid responsive and they remain oliguric or anuric.
- Once adequately filled, if hypotension persists then vasopressor support may be needed.
- Noradrenaline is commonly used to maintain a mean arterial pressure close to the patient's norm. However there is little evidence to suggest that pushing the blood pressure up higher has any benefits as this may lead to intra renal vasoconstriction, which is counterproductive.
- Consider an inotrope if there are concerns about the patient's cardiac output.

3. Medical management of AKI complications

Fluid balance

- A fluid restriction may need to be placed if the patient is oliguric; this may mean using a concentrated nasogastric feed and reducing the volume of fluid that drugs are given in.

- Ongoing fluid may be needed if the patient is polyuric.

Management of electrolytes

- There are a variety of electrolyte disturbances that can be seen, but the most important one acutely is hyperkalaemia. This should be treated appropriately and promptly. See PHT guideline for management of hyperkalaemia. (Also see Figures 5, 6).
- Any potassium supplements for hypokalaemia should be given cautiously

Principles of treatment of hyperkalaemia

1. Cardiac protection: antagonise the effect of potassium on excitable cell membranes
2. Redistribute potassium back into the cells (potassium is an intracellular ion)
3. Remove excess potassium from the body
4. Treat/correct underlying cause

Avoidance of secondary renal insults

- Further hypotensive events compromise renal perfusion, so limiting (or preventing) renal recovery.
- Regularly review the drug chart to avoid toxic side effects to the patient and to the kidneys.

Nutrition and glucose control

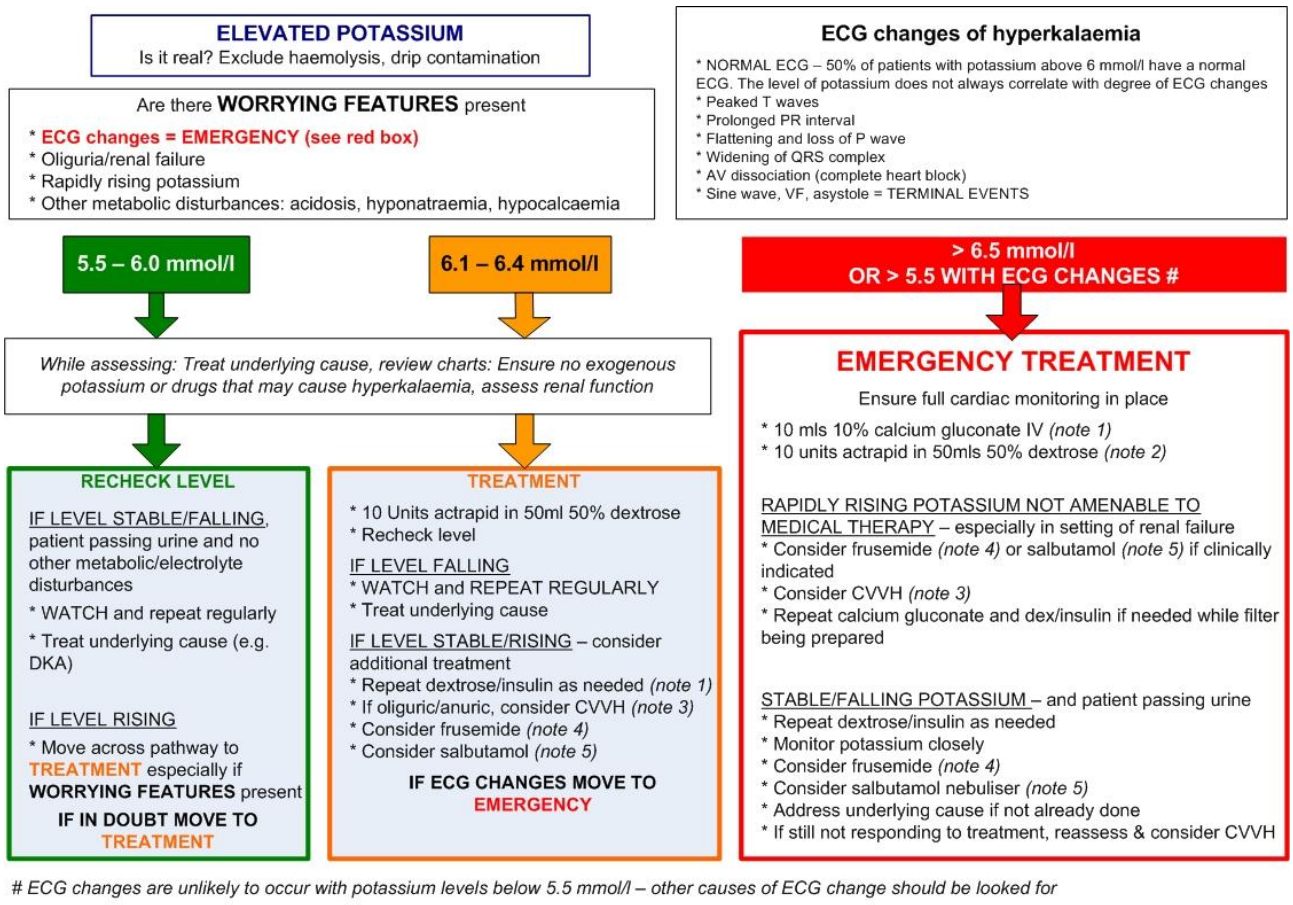
- All patients with renal failure should be fed; there is no role for protein restriction in critically ill patients on the intensive care unit.
- Glucose levels should be controlled as with all critically ill patients.

Bleeding

- Patients with advanced renal failure are at risk of bleeding. The exact cause is not known but is felt to be multi-factorial. One reason is due to abnormal platelet function – not their number, but how well they stick together.
- The risk of GI bleeding should be addressed with gastro-protection (ranitidine is fine unless there is a history of peptic ulcer/reflux disease in which case a proton pump inhibitor should be used) and early feeding – as with all ICU patients.
- DDAVP (desmopressin) can be used to treat uraemic ooze. Active surgical bleeding should be treated surgically, but DDAVP can be considered as a pre op adjunct in someone who has very high levels of urea. The mechanism of action is not fully clear, but one proposed action is that it acts by increasing the release of factor VIII and enhancing the expression of von Willebrand factor.
- Cryoprecipitate is rich in factor VIII, von Willebrand factor and fibrinogen and may be considered after DDAVP if bleeding still continues, in the setting of a normal INR/APTR – these should always be corrected first.

Dose of DDAVP: 0.3 - 0.4 mcg/kg in 50mls saline over 30 minutes intravenously – peak onset after about 1 hour. Multiple doses are not recommended due to tachyphylaxis.

Figure 5: Outline of management of hyperkalaemia on the Intensive Care Unit
(see also PHT guideline on treatment of hyperkalaemia)



 # ECG changes are unlikely to occur with potassium levels below 5.5 mmol/l – other causes of ECG change should be looked for

Note 1: Calcium gluconate

- *Use*: Cardiac membrane stabiliser – does not lower serum potassium
- *Dose*: Calcium gluconate 10 ml of 10% (2.20 mmol calcium/10mls). Give neat via central line over 5 minutes (2ml/min). If no central access, use a PATENT LARGE BORE CANNULA – flush well before and after use. Calcium chloride can be used: 10ml 10% contains 6.8 mmol calcium.
- *Action*: Onset less than 3 minutes. Effect lasts around 30-60 minutes. Further dose can be given after 5 minutes if ECG changes persist or changes worsen despite first dose.
- *Caution*: Extravasation leads to skin necrosis (Ca gluconate possibly less so than Ca chloride). If the patient is on digoxin then give 10 mls 10% diluted in 100 mls 5% glucose over 20 minutes (rapid calcium administration can precipitate myocardial digoxin toxicity).

Note 2: Dextrose and insulin

- *Use*: To shift potassium back into cells
- *Dose*: 10 units actrapid in 50 mls 50% dextrose over 5-10 minutes, flush well after use
- *Action*: Onset within 15 minutes with maximal effect after 30-60 minutes. Effect can last up to 4 hours. Can be repeated. If blood glucose is high initially (e.g. > 15 mmol/l) then insulin (e.g. 6 units actrapid) can be given without dextrose
- *Caution*: Blood glucose should be monitored regularly after administration

Note 3: Continuous renal replacement therapy

- *Use*: To remove potassium from the body
- *Dose*: CVVH or CVVHDF depending on the clinical state of the patient
- *Caution*: Hyperkalaemia especially with ECG changes should be treated medically first as it takes time to set up the haemofiltration machine

Note 4: Frusemide

- *Use*: To promote renal excretion of excess potassium
- *Dose*: 10-80 mg intravenously depending on the renal function of the patient
- Action: Onset of action depends on the degree of urine flow but is not immediate
- Caution: Ensure the patient is fully hydrated prior. Limited value if severe renal impairment as requires functioning renal tubules; no value if anuric

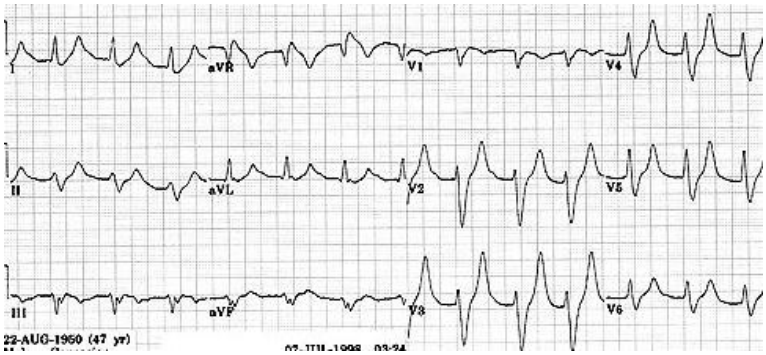
Note 5: Salbutamol

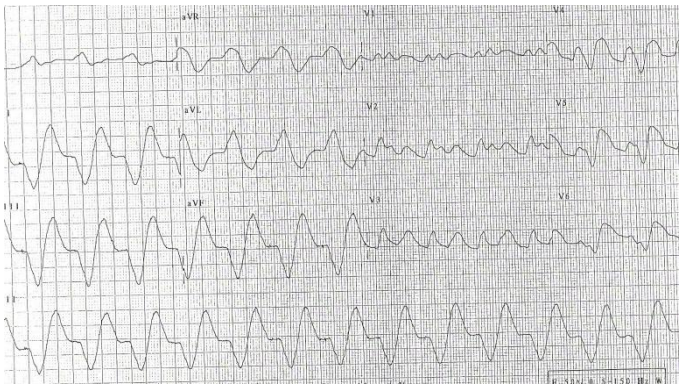
- *Use*: To shift potassium into cells
- *Dose*: 5-10 mg via nebuliser – there is no difference in efficacy between IV and nebulised salbutamol
- *Action*: 10 mg Salbutamol lowers potassium by 0.5-1.0 mmol/l over 15-30 minutes, lasting for up to 2 hours
- *Caution*: May cause tachycardia and precipitate arrhythmias. Effect is quite variable, and may not lower potassium in all patients.

Other notes:

1. *Sodium bicarbonate*: This leads to a shift of potassium into the cells. Generally only about 50 mEq at a time are given. It is not recommended as first line treatment except in a peri/cardiac arrest situation if a metabolic acidosis is present.
2. *Calcium resonium*: This is an anion exchange resin and is given orally or rectally. It can cause constipation and in extreme cases bowel necrosis. It tends to block nasogastric tubes and needs a functioning GI tract to work. IT SHOULD NOT BE USED ON THE ICU.

Figure 6: ECGs showing changes of hyperkalaemia (Top: peaked T waves. Bottom: More advanced changes)





Causes of hyperkalaemia

- Excess intake:
  - Exogenous source – Potassium supplements, large volume stored packed red blood cells, some drugs (e.g. penicillin G)
  - Endogenous source – rhabdomyolysis, massive haemolysis, tumour lysis syndrome, reperfusion syndrome
- Compartmental shifts:
  - Metabolic acidosis (e.g. diabetic ketoacidosis, lactic acidosis)
  - Insulin deficiency
  - Drugs (e.g. beta blockers, digoxin, succinylcholine)
- Renal causes:
  - Renal failure (acute or chronic)
  - Drugs (e.g. heparin, angiotensin converting enzyme inhibitors, angiotensin II blockers, ketoconazole, spironolactone, trimethoprim, ciclosporin, amiloride)
  - Mineralocorticoid deficiency (e.g. Adrenal insufficiency)
  - Renal tubular disorders and other rare conditions

For a full list of causes and pathophysiology refer to Up To Date via Intranet link

Contentious renal issues

Frusemide

In animal studies frusemide reduces the energy requirements of the cells in the thick ascending limb of the loop of Henle, and maintaining some urine flow may help 'flush out' renal casts. However there is no data to show that giving frusemide to a patient who has already developed an acute kidney injury alters the course of their kidney injury or reverses ATN any quicker. Frusemide itself is nephrotoxic and contributes to electrolyte disturbances. If fluid overload is the primary problem then frusemide can be used to improve fluid balance, however renal replacement therapy may be more appropriate.

Renal dose dopamine

Dopamine used at low doses improves renal blood flow in some situations. However patients respond in different ways to different doses of dopamine and 'low dose' may simply be acting to improve blood pressure rather than just improving renal blood flow. Dopamine has been associated with pituitary depression, immunosuppressive effects and cardiac arrhythmias. Importantly there is no evidence that renal dose dopamine alters the course of a patients acute kidney injury or reverses ATN any quicker.

Sodium bicarbonate

8.4% sodium bicarbonate can be used in the acute treatment of hyperkalaemia or for severe metabolic acidosis in a peri arrest situation. The downside of sodium bicarbonate is the sodium load and the risk of precipitating fluid overload. However when patients with renal failure are hypovolaemic and need fluid resuscitation, isotonic (e.g. 1.4%) sodium bicarbonate *may* be preferable to normal saline to avoid the risk of a hyperchloraemic acidosis. Isotonic sodium bicarbonate also has a role in the prevention of contrast nephropathy and in the fluid resuscitation of patients with, or at high risk of rhabdomyolysis.

Specific causes of acute kidney injury

1. Contrast induced acute kidney injury

Incidence and outcome
The overall incidence of contrast induced AKI (CI-AKI) is quoted at 3-7%, but it may be as high as 25% in high risk patient groups. However the true incidence is not known due to differences in definition and differences in patient populations studied. Most of the data is from out-patients or non ICU in-patients and particularly in those receiving intra arterial contrast. There is much discussion as to the true incidence of the condition on the ICU where most contrast is given intravenously (and dare I say, whether it actually exists?). Patients on the ICU are generally at high risk of AKI in general, and currently there are no biomarkers available that distinguish AKI due to contrast media from AKI due to say sepsis. The most commonly used definition so far is a rise in serum creatinine of 44 µmol/l or a 25% increase from the baseline occurring within 48 (sometimes 72) hours from having received iodinated contrast media. There have been calls to use the same definition and staging of AKI that is used for non-contrast AKI (RIFLE/AKIN/KDIGO). It is quite rightly pointed out that there is no reason why CI-AKI should have a separate definition.

The creatinine usually peaks at 5 days and returns to baseline by day 10. Renal failure is normally non oliguric but some will need renal replacement therapy.

The development of CI-AKI leads to an increased hospital stay and increased mortality; therefore efforts have focussed on preventative measures.

Risk factors for development of CI-AKI:

- Pre existing renal impairment with eGFR < 60 ml/min – this is the greatest risk factor
- Diabetes mellitus – particularly in combination with chronic kidney disease
- Intravascular volume depletion (e.g. dehydration) or effective volume depletion (e.g. congestive cardiac failure, nephrotic syndrome, liver disease)
- Left ventricular ejection fraction < 40%
- Concurrent use of nephrotoxic drugs (e.g. non steroidal anti inflammatory drugs, aminoglycosides)
- Type of contrast used (e.g. high volume, high osmolar) and route of delivery (intra arterial greater risk)
- Pre procedure shock (e.g. hypotension, intra aortic balloon pump)
- Increasing age

The risk of developing CI-AKI increases as the number of risk factors increases. In patients with a combination of risk factors the incidence of CI-AKI is reported to be as high as 25%.

Methods of prevention
As the development of CI-AKI is associated with increased morbidity and mortality there has been a great deal of work looking at methods of prevention. The findings are mixed, particularly when it comes to use of pharmacological agents. Most of the studies have been performed in out-patients or non ICU in-patients and it is not clear how applicable the findings are for high risk ICU patients. A CI-AKI Consensus Working Panel got together in 2006 and reviewed the evidence

available. They made a series of recommendations which can be extrapolated to include ICU patients.

- *Risk assessment*. Before any intravenous contrast is given in high risk patients the question should always be asked, is it really needed? If the scan with contrast is likely to provide benefits to the patient that will outweigh the risks then it should proceed, otherwise the scan should be performed without contrast.

- *Stop other nephrotoxic drugs*. This includes frusemide, non steroidal anti inflammatory agents and angiotensin converting enzyme inhibitors. Metformin should also be stopped.

- *Choice of contrast medium*. The smallest volume of a non ionic isosmolar contrast medium is the least nephrotoxic and should be used in high risk patients.

- *Intravenous hydration*.
  Volume expansion with intravenous fluid pre and post contrast is the one therapy that everyone agrees is beneficial in the prevention of CI-AKI. The exact mechanism as to how volume protects against CI-AKI is unclear, but may involve improvement of intrarenal haemodynamics and dilution of the contrast so reducing its adverse effects. A good urine output (> 150mls/hour) in the first 6 hours post procedure has been shown to reduce the incidence of CI-AKI, although in some ICU patients a urine output this good is not achievable.

  Which fluid to use, when to start it and how much to give is another story.

  Isotonic sodium bicarbonate or 0.9% sodium chloride pre procedure are the preferred fluid options currently.

  0.9% sodium chloride (normal saline) is commonly used and there is enough evidence to show it is superior to other concentrations of sodium containing fluids (e.g. 0.45%). Various 'protocols' have been used, but in practice clinical judgement should be used to ensure that the patient is adequately hydrated pre procedure and has fluids running during and post procedure.

  Isotonic sodium bicarbonate may be better due to better volume expansion, urinary alkalinisation and reduction of free radical mediated injury. There has been some interest in its use, with trial data suggesting some benefit over saline but not reaching a high grade of evidence so further studies are needed. The 'dose' of isotonic sodium bicarbonate (e.g. 1.4%) is 3ml/kg/hour for 1-2 hours pre procedure then 1-1.5 ml/kg/hour for 4-6 hours post procedure. Pre prepared isotonic bicarbonate can be used or it can be prepared at the bedside by adding 150mls of 8.4% sodium bicarbonate to 850 mls of 5% dextrose (giving ~ 1.2% sodium bicarbonate solution).

- *N-acetylcysteine (NAC).*
  NAC is an anti oxidant and although it is widely used, has generated a large number of small studies and an equally large number of meta analyses the results have been inconsistent and overall there is low quality evidence to support its use. NAC may falsely lower the serum creatinine without having any real protective effect on glomerular filtration rate. It is not a

substitute for adequate rehydration but it may give some protective effects when used in combination with fluid therapy in high risk patients. Work continues to try and determine who (if anyone) benefits from NAC and what the optimal dose/timing and route of administration is however until then NAC is still often recommended for 'high risk patients'.

Most of the studies have used oral NAC with some suggestion that a higher dose is better. The dose most often used is 600-1200mg orally twice a day for the day *pre* procedure then twice a day for the day *of* the procedure. The oral preparation is not always absorbed in ICU patients and often there is not enough time to load the patient pre procedure, so some would advocate that the oral dose of NAC be given intravenously. The evidence for oral vs intravenous NAC, like the evidence for NAC in general, is inconclusive but the incidence of side effects is less with oral compared with IV.

- *Other therapies*: Loop diuretics, mannitol and dopamine have all been used to prevent CN, however the evidence at best suggests no benefit and at worst suggests these therapies cause more harm than good.

- *Haemodialysis*. Contrast is removed by dialysis and studies have looked at the use of dialysis post procedure and shown some success. However dialysis is a costly, invasive procedure and is time consuming. So far its benefits have not outweighed the risks enough for it to be widely accepted. If however a patient is already receiving renal replacement therapy on the ICU it is sensible to put them back on the haemofilter after the contrast has been given to minimise the risks of the contrast on the already injured kidneys.

2. Systemic vasculitis

Vasculitis is an inflammation of blood vessels and the different types of vasculitis can be divided according to which size of blood vessel is predominately affected (figure 7).

Clinical features depend on the type of vasculitis (see following) but general symptoms can be very non specific: fever, myalgia, weight loss, night sweats. There is usually something else that points to the diagnosis of vasculitis, for example joint swellings, unexplained renal failure, pulmonary haemorrhage or a rash (figure 8). The rash seen in systemic vasculitis is due to the vasculitis affecting the skin blood vessels and it has a characteristic picture on biopsy. It can look similar to an early meningococcal rash but the history will differentiate. Drug reactions can mimic a vasculitis, but it should be remembered that drugs can cause a vasculitis. Finally marked thrombocytopenia can cause a rash which can be similar.

The diagnosis is made on the history and either supporting immunological tests (e.g. anti neutrophil cytoplasmic antibodies – ANCA) or a biopsy showing a vasculitis.

Figure 7: Classification of systemic vasculitis

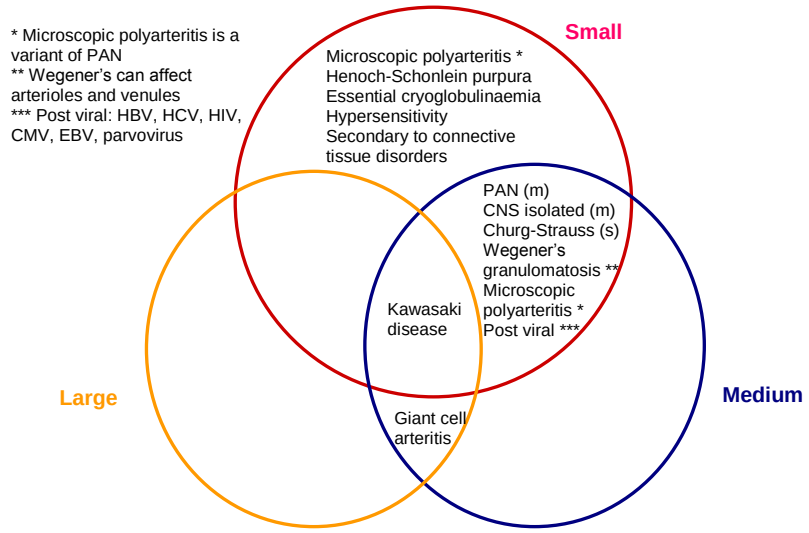
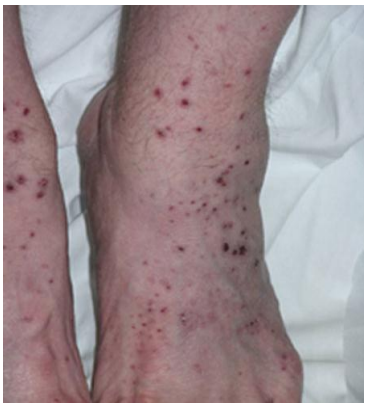


Figure 8: A vasculitic rash



ANCAs are something that are associated with vasculitis. They are auto antibodies directed against enzymes within the cytoplasm and the nucleus of neutrophils. These antibodies can then be divided into 2 groups, depending on immunofluorescence. Either C-ANCA or P-ANCA. Put simply, they light up differently when tested in the lab.

- *C-ANCA*: antibodies stain against enzymes in the cytoplasmic granules, mainly proteinase 3 (PR3). C-ANCA is strongly associated with Wegner's granulomatosis but is also seen with microscopic polyarteritis.
- *P-ANCA*: antibodies stain against the perinuclear cytoplasm and/or the nucleus, mostly the enzyme myeloperoxidase (MPO). P-ANCA is associated with microscopic polyarteritis, Churg-Strauss and polyarteritis nodosa, however P-ANCA is also seen in 'non vasculitis' conditions including rheumatoid arthritis, inflammatory bowel disease and primary sclerosing cholangitis.

It is not clear whether ANCA is a marker of disease or has something to do with the pathogenesis of the condition.

Goodpastures disease (anti glomerular basement membrane disease, anti GBM disease)

This condition affects all ages but with 2 peaks: young men (20-30 years) and older women (60-70 years). Antibodies are formed against the basement membrane of the lungs (causing pulmonary haemorrhage) and kidneys (causing renal failure).

10% of patients only have lung involvement, 20-40% only have renal involvement but 80% have lung and kidney involvement. Pulmonary haemorrhage is less common in non smokers, but also can be precipitated by fluid over load or infection. Renal involvement can be anything from proteinuria and microscopic haematuria through to rapidly progressive renal failure needing dialysis.

The diagnosis is made on the history, the presence of circulating anti GBM antibodies and characteristic findings on renal biopsy. Treatment is immunosuppression and therapeutic plasma exchange, especially if there is pulmonary haemorrhage.

Wegener's granulomatosis (WG)

This condition can affect the upper respiratory tract (ENT system), the lower respiratory tract and the kidneys, either alone or in combination. The condition can start just affecting the ear, nose and throat (limited disease) but can spread to affect other organ systems (generalised disease).

The diagnosis is made on a combination of a good clinical history, characteristic biopsy findings (e.g. kidney, nasal mucosa or lung biopsy) and the presence of C-ANCA. C-ANCA has a specificity of 90% for WG, however in limited disease it is only present in 50% but by the time the condition becomes generalised it is found in 95% of patients.

Common findings at presentation:

- ENT: e.g. sinusitis, bloody nasal discharge (90%)
- Renal: e.g. microscopic haematuria, renal failure (90% - 40% are dialysis dependant)
- Lung: e.g. pulmonary nodules, infiltrates on CXR, pulmonary haemorrhage, cavitating lesions (90%)
- Musculoskeletal (80%)
- Eye: e.g. conjunctivitis, episcleritis (60%)
- Neurological: peripheral neuropathy, CVA, fits (50%)
- Rash (50%)

Treatment is with immunosuppression. With treatment 1 year survival is 50-70% depending on the severity of the presentation. 30% can progress to end stage renal failure if they have abnormal renal function on presentation.

Microscopic polyangiitis

This is a small vessels vasculitis that primarily affects the capillaries of the kidneys (glomeruli) or the lungs. It most commonly presents with renal failure but can lead to pulmonary haemorrhage. 70% of patients are ANCA positive, mostly P-ANCA. Presentation may be very similar to WG but the diagnosis is made on ANCA testing and biopsy. Treatment is with immunosuppression and plasma exchange if pulmonary haemorrhage is present.

3. Rhabdomyolysis

Rhabdomyolysis is the breakdown of muscle fibres with the subsequent release of toxic muscle products and electrolytes into the circulation. Renal failure develops in about 15-70% of cases depending on the cause and the severity of the condition. There is a long list of causes (table 7).

Table 7: Causes of rhabdomyolysis (commonest on ICU in red)

Physical	Trauma, hyperthermia, hypothermia, strenuous exercise, prolonged fitting, electric shock
Toxins and drugs	Alcohol, statins, amphetamines, ethylene glycol, ecstasy, snake bites
Infection	Long list of viral, bacterial and fungal infections including influenza, HIV, tetanus, strep pneumoniae, mycoplasma
Metabolic	Hypernatraemia, hyponatraemia, hypokalaemia, DKA, diabetic hyperosmolar coma, malignant hyperpyrexia
Inherited	Muscle enzyme disorders, Wilsons disease
Inflammatory	Polymyositis, dermatomyositis
Vascular	Vascular compromise (occlusion or severe hypoperfusion), sickle cell disease, high dose vasoconstrictors

Diagnosis

Muscle necrosis leads to the release of muscle components into the circulation:

- *Creatinine kinase* (CK). This is often extremely elevated, often over 5 times the upper limit of normal. CK levels should peak by 24 hours and start to fall by about 40% per day. If the levels continue to rise, or remain elevated, then ongoing muscle injury should be looked for and in particular the presence of compartment syndrome. Compartment syndrome is where inflammation in a muscle compartment leads to swelling so compromising blood and nerve supply and leading to more muscle necrosis. Treatment is with early fasciotomies.
- *Myoglobin*. This can be detected in the urine and it is classically felt to be diagnostic of rhabdomyolysis, however myoglobin is not detected in around 18-50% of cases.
- *Other muscle enzymes*. Aspartate transaminase (AST) and lactate dehydrogenase (LDH) may also be elevated.

There are other characteristic biochemical and metabolic features:

  - Marked *hyperphosphataemia.*
  - *Hyperkalaemia* due to leakage of potassium from damaged cells.
  - Metabolic acidosis due to increased lactate release by damaged muscles.
  - Hypocalcaemia due to the movement of calcium into the damaged muscle cells. As the muscle cells start to recover then the calcium moves back out again and so plasma calcium levels can then go up.

Mechanism of renal injury

- Myoglobin that is released by damaged muscle cells is directly toxic to the renal tubules as well as having effects on blood flow within the kidney. Myoglobin also binds to a protein found in the renal tubules and forms casts which precipitate in the tubules in acidic conditions.

- Fluid shifts can lead to intravascular volume depletion which can further compromise renal function.
- Diuretics, including mannitol have been suggested to 'flush out the casts', but there is little evidence to support its use and it can cause more harm than good if the patient is not fully fluid resuscitated in the first place.

Treatment

- Prevention is the key. Adequate volume resuscitation soon after the insult (in cases of trauma or surgery) or as soon as the diagnosis is made is the only therapy that has been definitely shown to be effective. Large volumes of fluid are often needed, the choice of fluid, as you might expect, is debated.
- Myoglobin is less soluble in an alkaline environment (urine pH > 7) therefore isotonic bicarbonate solution (e.g. 1.4%) is often used to alkalinise the urine as well as improve intravascular volume status. Myoglobin is rapidly cleared by the kidneys if they are functioning, therefore all efforts should be made to maintain renal perfusion. Renal replacement therapies such as haemofiltration are able to remove some myoglobin but there is no strong evidence to suggest that RRT has beneficial effects on renal function once rhabdomyolysis has occurred.
- It is tempting to treat the initial hypocalcaemia but intravenous calcium should only be used if there are symptoms of hypocalcaemia. This is due to the risk of rebound hypercalcaemia as calcium moves out of muscle cells once they start to recover.

Outcome

- If the patient survives the initial insult the renal function returns to normal by 3 months in almost all cases.
- Mortality is related to the causative condition.

Continuous renal replacement therapy

Indications for renal replacement therapy on the ICU

About 6% of critically ill patient require renal replacement therapy, and there are a number of reasons why it may be started (table 8):

Table 8: Indications for renal replacement therapy

- ✓ A rapidly rising urea and creatinine
- ✓ The development of uraemic complications
- ✓ Hyperkalaemia unresponsive to medical treatment
- ✓ Severe metabolic acidosis
- ✓ Diuretic resistance pulmonary oedema
- ✓ Oliguria or anuria
- ✓ Removal of ingested toxins
- ✓ To correct electrolyte abnormalities
- ✓ Possible removal of inflammatory mediators in sepsis

∗ *A rapidly rising urea and creatinine*

Creatinine has limitations when using it as a marker of glomerular filtration rate (GFR) as it does not always accurately reflect functioning renal mass and changes in plasma levels lag behind changes in GFR. It is also affected by non renal factors such as age, sex, race, lean body weight and muscle mass. Remember creatinine does not rise till the GFR has fallen by 50%.

Urea is commonly measured but is not the only uraemic toxin. Its production is affected by protein intake (including upper gastrointestinal bleeding), state of catabolism, volume status and corticosteroids. Therapy should be started before the urea is greater than 20-30mmol/l in acutely ill ICU patients but the rate of change of urea and creatinine are as important as their absolute levels and this should be considered together with the patient's clinical condition as a whole.

∗ *The development of uraemic complications*

Classic uraemic complications such as nausea, vomiting and encephalopathy are often hard to spot on sedated ventilated patients. However severe uraemia affects platelet function and may contribute to problems with bleeding.

∗ *Hyperkalaemia unresponsive to medical management*

There is no 'upper limit' of potassium to guide when to start RRT, the patient's clinical state as a whole needs to be considered. It is however still quicker to initially treat the hyperkalaemia medically with calcium gluconate and dextrose/insulin rather than to wait till a haemofiltration machine has been set up.

∗ *Severe metabolic acidosis*

There is no 'lower level' of pH to guide when to start RRT, again the patient's clinical state as a whole needs to be considered.

∗ *Oliguria or anuria*

Fluid balance is a common reason for starting RRT on the ICU. Critically ill patients often need large volumes of fluid and may develop clinically significant fluid overload needing RRT. Renal replacement therapy may be used to improve the overall fluid balance status of patients.

Oliguria is a good marker of deteriorating renal function but it can be affected by other factors such as body size, solute intake and use of diuretics. As with biochemical results, urine output should be interpreted in light of the patient's clinical condition. A standard definition of oliguria is a urine output of less than 0.5mls/kg of body weight per hour for more than 6 hours.

∗ *To correct electrolyte abnormalities*

As mentioned, hyperkalaemia resistant to medical therapy is an indication to start RRT. There are reports of CRRT being used (in exceptional circumstances) to treat sodium disturbances.

∗ *Potential removal of inflammatory mediators in sepsis*

The removal of inflammatory mediators in sepsis will be discussed in further detail later.

∗ *Removal of ingested toxins*

Not all ingested toxins are removed by renal replacement therapy; it depends on their size and degree of protein binding.

Toxins can be removed by:

a. Intermittent haemodialysis – this is good for low molecular weight water soluble toxins with low protein binding and a low volume of distribution. The degree of clearance depends on the haemofilter membrane surface area (bigger is better) as well as blood and dialysate flow rates. Removal is quick but there is the risk of rebound toxicity when you stop the therapy due to redistribution of the toxin.

b. Continuous renal replacement therapy (haemofiltration, haemodiafiltration) – this is good for water soluble toxins with low protein binding and a low volume of distribution. It removes larger molecules better than intermittent haemodialysis. Although toxin removal is slower there is less risk of rebound toxicity.

c. Haemoperfusion – this is where blood passes through a cartridge that contains a material that can absorb the toxin. There are 3 types of sorbents: charcoal based (not good for protein bound toxins), synthetic resin and anion exchange resins (both good for protein bound toxins and lipid soluble molecules). Haemoperfusion is technically more difficult to do than haemodialysis and therefore is not universally available.

Examples of drugs able to be removed via CRRT include barbiturates, lithium, salicylates, theophyline, ethylene glycol and methanol. Specialist advice should be sought e.g. Toxbase.

Timing of therapy

There are no universally accepted levels of urea, creatinine, potassium or pH at which to start therapy. There is however increasing support for starting RRT sooner rather than later, but how you define early or late is a point of discussion. Studies have used solute levels (absolute levels as well as grade of AKI) and urine output as well as day of ICU admission as start points. Each has its limitations, but above all the reasons for starting therapy are often multifactorial and hard to separate out. Fluid overload (an important reason for starting therapy) is also very hard to quantify.

Intermittent versus continuous therapies

The terms dialysis and haemofiltration (or filtration) are often used interchangeably, but traditionally 'dialysis' suggests an intermittent therapy and 'haemofiltration' refers to a continuous therapy.

Intermittent therapy

Also known as intermittent haemodialysis (IHD), this is the therapy typically provided on the renal unit to patients with AKI or those with end stage renal failure needing chronic dialysis. As the name implies, it is intermittent and is very efficient at clearing toxins. Typically done for 4 hours at a time 3-4 times a week, IHD uses different dialysis machines compared to those used on the ICU and ultra pure water to 'make' the dialysis fluid from a concentrate rather than using pre prepared bags of fluid. The blood flows on IHD are significantly higher than those used on the ICU, and therefore the patient needs to be relatively robust to tolerate it.

Continuous therapy

As the name suggests, continuous renal replacement therapy (CRRT) is continuous, or at least it is meant to be. It is designed to run continuously as it clears solutes slower than IHD. CRRT is delivered by the bed side ICU nurse and uses pre prepared bags of fluid. Blood flows are lower than IHD and fluid removal slower; therefore as a consequence it is often better tolerated by haemodynamically unstable patients. CRRT is often (inaccurately) called haemofiltration.

Intermittent versus continuous therapy

Over the years there has been extensive debate as to whether CRRT is superior to IHD to treat critically ill patients on the ICU. It was previously thought that critically ill patients had a worse outcome when treated with IHD compared to CRRT; however a Cochrane review and other meta analyses have found that there is no difference between the 2 therapies.

The advantages of IHD are related to cost and being able to fit in therapy between trips to the CT scanner and theatre, however not all ICUs have the ability to perform IHD (due to equipment and staff expertise).

It is not really a case of which therapy is best, but which therapy is best for that particular patient and which therapy can be delivered in that setting. Most clinicians choose a continuous therapy for their haemodynamically unstable patients on the ICU and it is by far the most common form of therapy on ICU's in the UK and this handbook will concentrate on continuous therapies.

Mechanism of solute removal

Having decided that the patient needs renal replacement therapy, and having chosen continuous therapy, the next step is to choose the *type* of continuous therapy. The common types of CRRT used on the ICU are:

CVVH – Continuous veno-venous haemofiltration
CVVHD – Continuous veno-venous haemodialysis
CVVHDF – Continuous veno-venous haemodiafiltration
SCUF – Slow continuous ultrafiltration (this is a method of water removal, not solute removal)

Difference between therapies

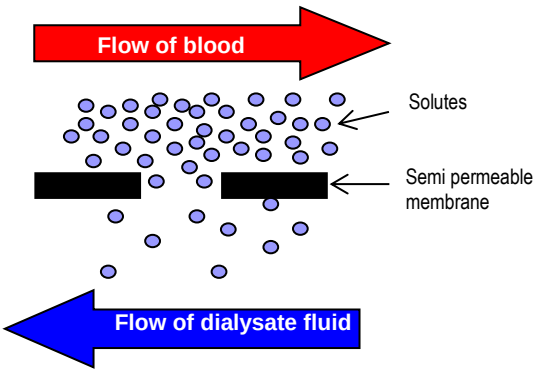
All forms of therapy remove urea, creatinine, potassium, acid, fluid etc, but they differ in the *way* that they remove solutes. To understand the differences it is important to understand firstly that there are different sizes of solutes (small, middle and large, see table 9) and that different solutes are removed (mostly) by 2 different processes (diffusion and convection).

Table 9: Size of solutes removed by renal replacement therapy

	Examples
Large molecules (> 5,000 Daltons)	Albumin other large proteins
Middle molecules (500-5,000 Daltons)	B_2 microglobulin, cytokines, inflammatory mediators
Small molecules (< 500 Daltons)	Urea, creatinine, phosphate, potassium

Diffusion

This is the movement of solutes from an area of high concentration (the patient's blood) to an area of low concentration (dialysis fluid) across a semi permeable membrane (the haemofilter). Given enough time, then the concentration of solute would eventually become the same on both sides, therefore to maintain this concentration gradient blood flows in one direction and fresh dialysate fluid flows in the opposite (counter current) direction.

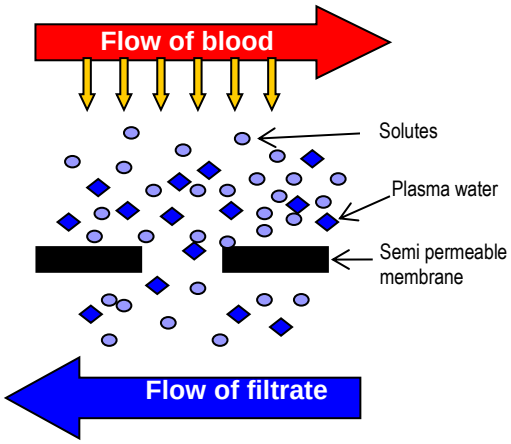


The rate of solute removal by diffusion is related to:

- The thickness of the (haemofilter) membrane
- The size of the pores in the membrane (the surface area)
- The electrical charge of the solute to be removed
- The size of the solute to be removed (diffusion is very effective at removing small molecules)
- Maintenance of the concentration gradient (i.e. having a counter current flow)

Convection

If a pressure gradient is generated across the semi permeable membrane (haemofilter), then water from the patient's plasma is forced across the membrane from one side to the other (ultrafiltration). As the plasma water (ultrafiltrate) moves across, it carries dissolved solutes with it. This is called a solvent drag. The ultrafiltrate that is produced, by now called effluent is then got rid of (in the sluice!). The size of molecule that can be removed this way depends on size and molecular charge.



The rate of solute removal by convection is related to:

- The size of the pores in the membrane (the surface area)
- The electrical charge of the solute to be removed
- The size of the solute to be removed (convection is very effective at removing middle molecules as well as small molecules)
- Maintenance of the pressure gradient across the haemofilter membrane by:
  - Increasing blood flow rate (in other words making the pressure more positive on the blood side)
  - Making the pressure more negative on the other side (for example by increasing the effluent production rate)
  - Decreasing the oncotic pressure of plasma (for example by giving the replacement fluid before the filter – pre dilution)

Method of solute removal by different therapies

The way that solutes are removed in different therapies is shown in table 10. All types of treatment are able to remove water, and the removal of just water is called ultrafiltration (UF).

Table 10: Method of solute removal by therapy

CVVHD	Diffusion
CVVHDF	Diffusion and convection
CVVH	Convection

Convection versus diffusion

As all therapies are capable of removing urea, creatinine, potassium, acid and water you could say does it really matter which therapy we choose? CVVH (convection) will clear solutes slowly and CVVHDF (convection and diffusion) will clear them a little quicker. Studies done looking at dose of therapy (see later) have not concentrated on the method of solute removal as such, but as convective therapies are probably better at clearing middle molecular weight molecules (as the kidney does) then the question probably needs to be formally answered – is there any difference in outcome between convection and diffusion?

Types of CRRT therapy

The basic extracorporeal circuit

1. Blood comes out of the patient through a **dialysis catheter**. It is pumped around the haemofiltration machine by a roller pump at a speed that is set by the operator.
2. The blood goes through a series of **monitors** to keep an eye on the pressure and make sure that no air gets into the circuit. These are all safety mechanisms to protect the patient and so may lead to the triggering of an alarm.
3. The blood goes through a **haemofilter**: The haemofilter is made up of thousands of hollow fibres bundled together, through which blood passes. The fibres themselves are made of a semi-permeable material with pores (holes) of a certain size. The haemofilter will be discussed a bit later but the benefit of having all these hollow fibres is that it increases the surface area of the filter so there is a bigger area across which solutes can move.
4. The blood is then pumped back to the patient - this is the basic extracorporeal circuit and it continues round and round.

Continuous veno-venous haemodialysis (CVVHD) circuit [Figure 9a]

Now consider adding a second circuit to the system. Fluid (dialysate) circulates in the opposite direction to the flow of blood in the basic extracorporeal circuit. This fluid passes through the haemofilter, but *outside* the hollow fibres, bathing the blood passing *through* the fibres in the opposite direction. Solutes such as urea, creatinine and potassium move from the patient's blood (an area of high concentration) to an area of low concentration (the circulating dialysis fluid) across the wall of the hollow fibre (a semi permeable membrane). This is the process of *diffusion*. Fresh dialysis fluid is continually circulated round at a rate set by the operator (for example 2500mls/hour). As this dialysis fluid, by now carrying waste products (and therefore called effluent) leaves the haemofilter, it is collected in a bag and then discarded. This is CVVHD.

Continuous veno-venous haemofiltration (CVVH) circuit [Figure 9b]

Go back to the basic extracorporeal circuit but this time create a pressure gradient across the haemofilter as the blood goes through. Due to the pressure created, a desired volume of plasma water is pumped out of the patient's blood (for example 2000mls/hour) and passes through the holes in the haemofilter membrane. This plasma water carries with it solutes such as urea, creatinine and potassium. This is the process of convection. The waste plasma water containing dissolved solutes (called effluent) is then discarded. However, you can image that if you are discarding 2000mls/hour (for example) of plasma water then the patient would very rapidly become dehydrated. Therefore this volume of plasma water is 'exchanged' for specialised replacement fluid, at a rate that either matches the volume of water removed (neutral balance) or is less than that removed (for fluid removal). Replacement fluid will be discussed a little later, but in practice it is the same composition as dialysis fluid. This process of removing plasma water and solutes by convection and then replacing it with specialised fluid is called CVVH.

Figure 9a: Continuous veno-venous haemodialysis circuit (CVVHD)

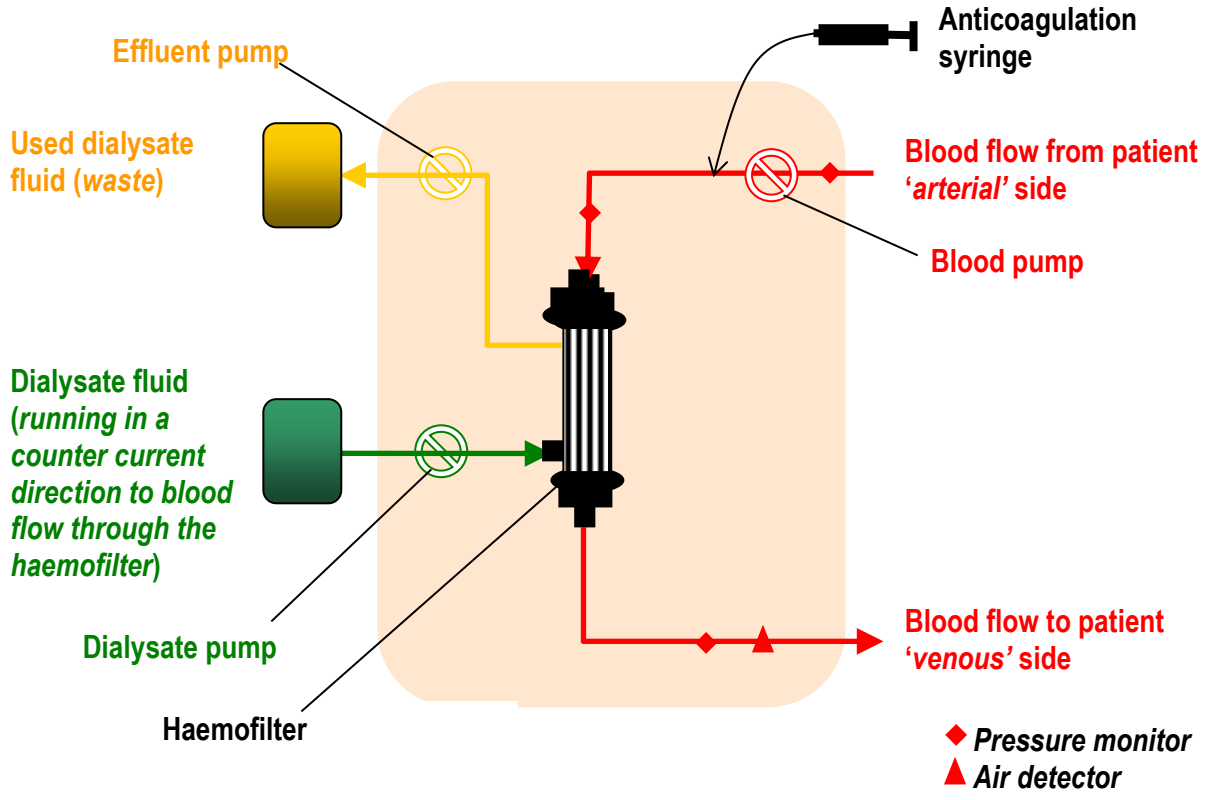
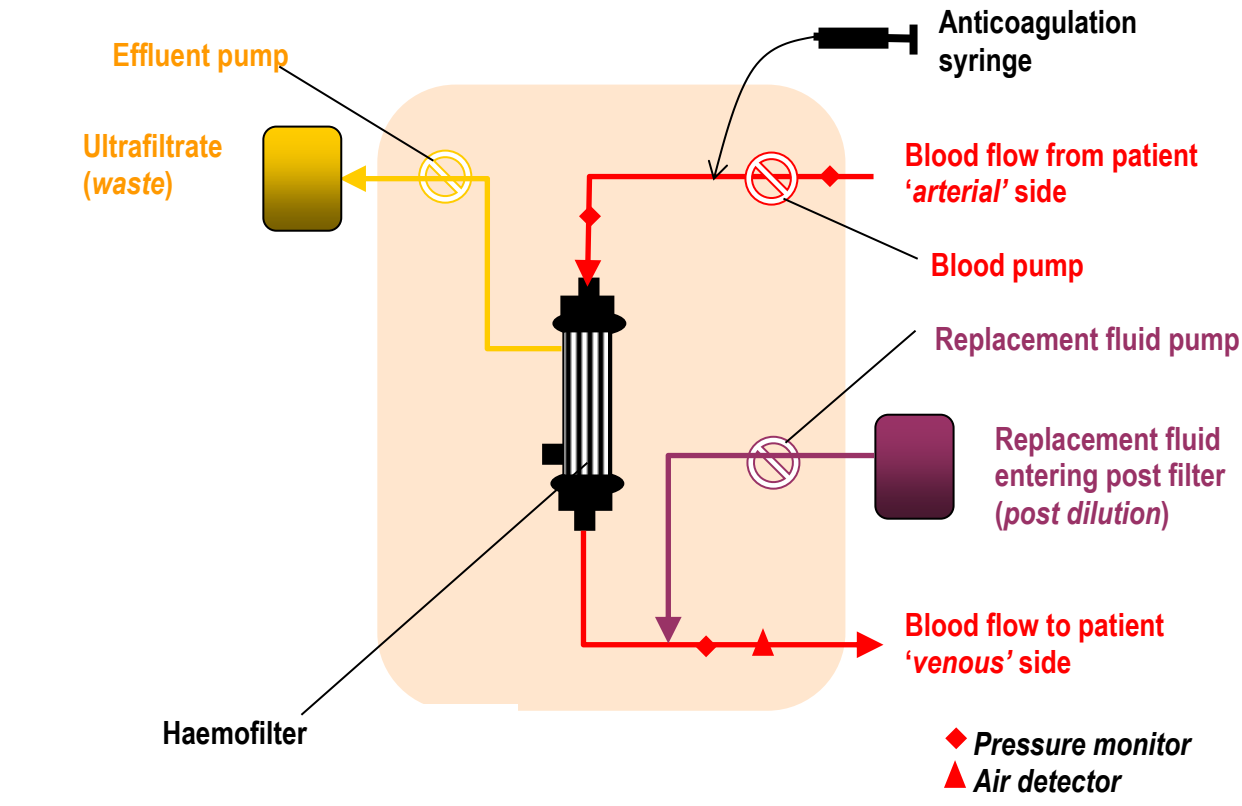


Figure 9b: Continuous veno-venous haemofiltration circuit (CVVH)



Continuous veno-venous haemodiafiltration (CVVHDF) circuit [Figure 9c]

If you then combine the above two circuits and have circulating dialysis fluid *and* remove plasma water *and* replace it with a specialised fluid, you get solute removal by diffusion and by convection. This set up is CVVHDF.

Slow continuous ultrafiltration (SCUF) circuit [Figure 9d]

All of these methods are able to remove solutes and water. If you just wanted to remove water, for example if a patient was extremely fluid overloaded, then the circuit can be set up just to remove water (the process of ultrafiltration). There is *no* circulating dialysis fluid and the water that is removed is *not* replaced by specialised fluid, this is the process of SCUF.

In summary

CVVH: Continuous veno-venous haemofiltration – removal of plasma water leads to the removal of solutes via the process of convection, and the ultrafiltrate is then replaced by fresh replacement fluid.

CVVHD: Continuous veno-venous haemodialysis – dialysate fluid is circulated past the patient's blood and solutes are removed via the process of diffusion. No replacement fluid is infused.

CVVHDF: Continuous veno-venous haemodiafiltration – removal of plasma water leads to the removal of solutes via the process of convection, and the ultrafiltrate is replaced by fresh replacement fluid. ALSO circulating dialysate fluid removes solutes via the process of diffusion.

SCUF: Slow continuous ultrafiltration – this is the removal of water only; minimal concentrations of solutes are removed.

Figure 9c: Continuous veno-venous haemodiafiltration circuit

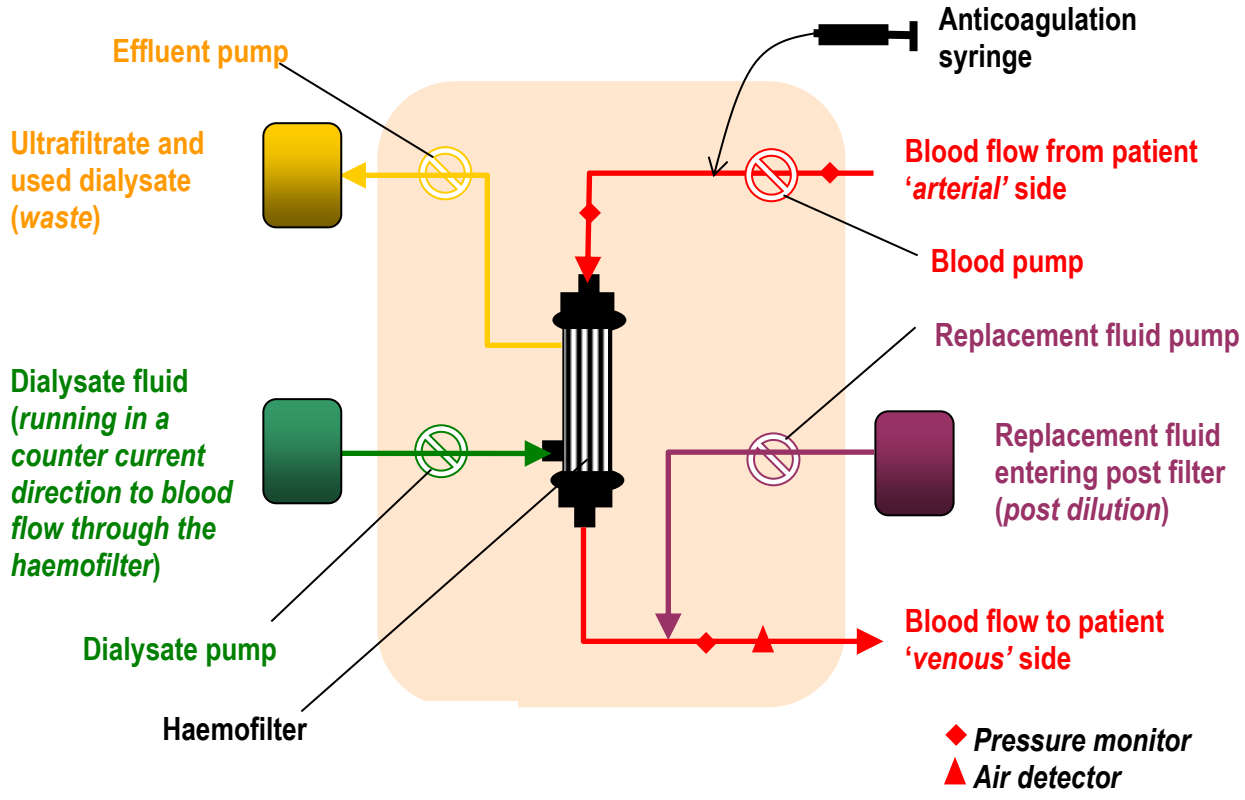
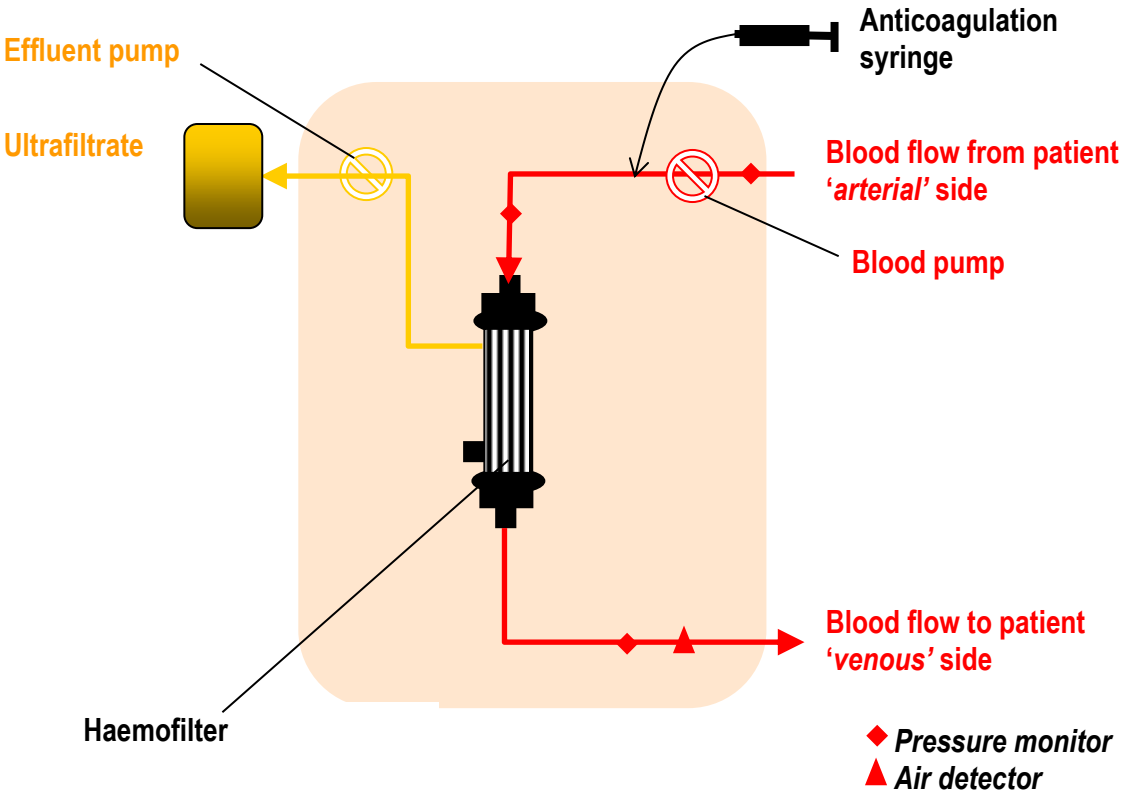


Figure 9d: Slow continuous ultrafiltration circuit



Extracorporeal flow rates and the concept of dose

The purpose of CRRT is to remove solutes and water from the blood. *Clearance* of a solute is the volume of blood that is completely cleared of solute in a unit of time (e.g. mls per minute). Different solutes are cleared by the haemofilter in different ways: diffusion and/or convection as discussed earlier.

Factors affecting how well or how much of a solute is removed are:

- The *method* of solute removal: diffusion and/or convection
- The *size* of the solute to be removed: small, middle or large
- Characteristics of the haemofilter membrane (to be discussed later)
- Extracorporeal flow rates: blood flow rate, ultrafiltration flow rate (how much plasma water is removed by convection) and dialysate flow rate

It can be seen that there are a number of settings that can be adjusted depending on which mode you choose. Table 11 shows which settings need adjustment according to each mode.

Table 11: Flow rates that need setting according to mode of therapy

	Blood flow rate	*Replacement fluid rate*	*Dialysate flow rate*	*Patient fluid removal rate*
CVVH	Y	Y	N	Y
CVVHDF	Y	Y	Y	Y
CVVHD	Y	N	Y	Y
SCUF	Y	N	N	Y

1. Blood flow rates

This is the rate that blood is pumped out of the patient, through the machine and then back to the patient again. It is abbreviated as Qb and is measured in mls/min.

For all therapies (except SCUF) the ideal blood flow rate is a minimum of 150-180ml/min (generally up to 250mls/min depending on ultrafiltrate rates).

The importance of good blood flow

A proportion of plasma water is removed from blood as it passes through the filter (filtration fraction – see below) making the blood more 'concentrated'. Haemoconcentration can lead to sluggish flow through the hollow fibres which may lead to micro blood clots forming within the filters. Initially this just makes the haemofilter less effective but if this continues then the whole haemofilter can clot and can no longer be used. A slow blood flow not only promotes clotting within the filter but also leads to stagnant blood around the end of the dialysis catheter which again can lead to blood clot formation around and within the tip of the dialysis catheter. A good blood flow through the filter helps to open up the filaments better and so makes the filter more efficient.

When using a mode which employs dialysate fluid, the fluid circulates through the haemofilter in the opposite direction to the flow of blood. This 'counter current' system is to make sure that

there is always a concentration gradient between blood which has a high concentration of solutes, and the dialysate fluid which has a lower concentration of solutes.

Filtration fraction

This is the fraction of plasma water that is removed from blood each time it passes through the filter during convective therapy; too much fluid removal and excessive haemoconcentration occurs. The filtration fraction should be less than 20-25%, but certainly less than 30%. In other words, each time the blood passes through the filter, 20-25% of the plasma water is removed – remembering that blood is made up of cells (haematocrit) *and* plasma water.

If the filtration fraction is too high the blood flow rate should be increased. If this is not possible, then the ratio of pre to post dilution can then be adjusted, with a greater percentage going pre dilution. But remember, pre dilution helps to reduce the haematocrit but at the expense of less solute clearance.

Filtration fraction = $\frac{\text{Ultrafiltration rate (ml/min)}}{\text{Plasma flow rate (ml/min)}}$ *(x 100 to convert to %)*

Plasma flow rate = blood flow rate (ml/min) x (1-haematocrit)

Can high blood speeds make the patient hypotensive?

There are various reasons why patients drop their blood pressure on the filter, not necessarily related to the blood flow rate. The whole circuit (blood tubing and within the haemofilter) takes about 150 mls of blood. The circuit will have been primed with saline so they are not 'losing' volume; they are having 150 mls of blood passing out of their body and being replaced with 150 mls saline. Some patients will be very haemodynamically unstable and a few may not tolerate this however for most patients once the circuit is up and running (as it is a closed circuit) they will tolerate higher blood flow rates and other reasons should be looked for to explain the drop in blood pressure (see later).

2. Replacement fluid rate

This is the volume of replacement fluid that is replacing the volume of plasma water removed per hour (sometimes called an exchange) and is set in CVVH and CVVHDF mode. As outlined before, the plasma water that is being removed carries with it solutes (urea, creatinine, potassium etc). If you remove more plasma water (effluent) then you clear more solutes. For quite some time 1-2l/hour replacement fluid rate was considered the standard, however in order to 'dose' continuous renal replacement therapy, the volume of effluent that was being produced was referred to.

3. Effluent fluid rate

The effluent that is produced is either waste plasma water containing solutes (CVVH), waste dialysis fluid containing solutes (CVVHD), or is a mixture of both if using CVVHDF. Either way, the effluent that is produced contains waste products and is analogous to urine. In the way that the kidneys clear a certain volume of solutes from the blood in a period of time (glomerular filtration rate) the haemofiltration machine also clears a certain volume of solutes in a period of time. The volume of effluent produced per hour can be indexed to the patient's body weight giving a 'dose' of ml/kg/hour of effluent production (see following). It is sensible to adjust to the patient's body weight in the same way we dose vasopressors and inotropes to body weight, to take in to account the varied size of patients that are seen on the ICU.

4. Dialysate fluid rate

This is the volume of dialysate fluid that circulates past the blood per hour and is set in CVVHD and CVVHDF. To provide the best conditions for diffusion (i.e. to maintain the right diffusion gradient) then dialysate flow rate (in ml/min) should be at least double the blood flow rate (in ml/min). When using CVVHDF the dialysate to replacement fluid rate is 1:1 – in other words, 50% of your chosen effluent flow rate is delivered as dialysate and 50% as replacement fluid.

The 'dose' story

The main starting point was Ronco's 2000 study that looked at different 'doses' of effluent production in patients on the ICU, they found that those who had 35mls/kg/hour of effluent removed had a better survival compared to those who only had 20ml/kg/hour and so 35mls/kg/hour of effluent production entered ICU practice.

This was then followed by a whole series of other studies looking at whether this was the optimal dose. Some came down in favour of a higher dose (35mls/kg/hour or more) and some came down in favour of a lower dose (around 20ml/kg/hour). Each study has its strengths and weaknesses, but the studies were not standardised for timing of therapy, mode of therapy (convective/diffusive clearance) and different doses were compared. This led to the call for a large, well conducted randomised controlled trial.

In 2008 the ATN study (Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury) looked at intermittent and continuous therapy at either a high or low intensity (35 versus 20 mls/kg/hour effluent production for CRRT using CVVHDF). They did not find any difference in outcome between high or low intensity therapies.

In 2009 the RENAL study (Randomised Evaluation of Normal versus Augmented Level of Renal Replacement therapy) published their findings. They found that there was no difference in outcome between 40 and 25mls/kg/hour effluent production using post dilution CVVHDF.

Very shortly after, 2 meta-analyses were produced that confirmed that there was no difference in outcome between high intensity therapy (35-48mls/kg/hour) and low intensity therapy (20-25mls/kg/hour).

The studies that have been done use prescribed or actual effluent production volume as a surrogate for solute clearance, but there are a few observations that need to be raised with respect to all the studies that have been done. Regarding **actual** solute clearance there are operational characteristics that may affect solute clearance in addition to 'mls/kg/hour' and it should be remembered that the only real way to know how much solute is being cleared is to measure it.

Prescribed versus delivered dose

As we all know from clinical practice, continuous therapy is not always continuous. There may be elective periods of downtime (e.g. for imaging) or unintentional periods of downtime (e.g. filter clotting, dramatic change in the patients clinical state). The delivered dose (for CRRT) in the ATN and RENAL studies was (respectively) 89% and 84% for intensive therapy and 95% and 88% for less intensive therapy. So it can be seen that even in the setting of a trial, compliance is never going to be 100%. Therefore it should be remembered that whatever prescribed dose is being used, the delivered dose is going to be lower.

Use of pre dilution

In clinical practice, as well as in the trials, the use of pre dilution versus post dilution (and percentage of each) is variable. Pre dilution will reduce solute clearance; therefore although the prescribed dose may be the same, the actual solute clearance may be affected.

Choice of modality

Again, in clinical practice as well as in the trials there is a variation in the choice of modality in the UK but generally CVVH (convective clearance only) or CVVHDF (convection and diffusive clearance). There are no studies comparing outcome using the different modalities and looking at the dose studies that have been done over the years they range from CVVH only (Ronco) to SLED/CVVHDF (ATN) to CVVHDF only (RENAL). We therefore don't really know if it does (or does not) matter which therapy you use.

More to renal failure than just urea

The dose of effluent is a surrogate for urea clearance but the indications for starting CRRT are not just based on urea levels. Lifesaving therapy for one patient may well involve clearing a large urea load, for another it may be potassium removal and for another it may be fluid removal. It may be rather simplistic (but easier for trials) to think that we can condense all that into one number.

Sepsis and high volume haemofiltration (HVHF)

Inflammatory mediators such as tumour necrosis factor and interleukin 6 fall into the category of 'middle molecular weight' molecules and it has been shown that it is possible to remove them by renal replacement therapies, particularly convective therapies. This led to interest in whether this property can be used as an adjunct in the treatment of septic shock.

Severe sepsis is characterised by the release of a cascade of pro *and* anti inflammatory mediators and it is unrealistic to think that RRT will simply just remove the nasties. Its effect is most likely through some means of immunomodulation. Given that a large cascade of inflammatory mediators will be released in severe sepsis, a large volume of ultrafiltrate will need to be produced, certainly more than the standard volume of ultrafiltrate. This gave rise to the concept of high volume haemofiltration (HVHF). What is meant by 'high volume' was open to interpretation, but a consensus conference defined HVHF as continuous high-volume treatment with an effluent rate of 50–70 mL/kg/hour (for 24 hours per day) or intermittent very high-volume treatment with an effluent rate of 100–120 mL/kg/hour for a 4–8 hour period followed by conventional 'renal-dose' hemofiltration.

Initial reports suggested that there was a short term improvements in haemodynamic stability, however studies were never large enough to be able to detect any outcome benefits. In 2013 the long awaited IVOIRE study (hIgh Volume in Intensive caRE) was published comparing high volume CVVH (70ml/kg/hour) with standard volume CVVH (35mls/kg/hour) in septic shock patients with an acute kidney injury. A multi-centre randomised trial, it was unfortunately stopped early due to poor recruitment, however they found that there was no difference between standard and high volume haemofiltration with regard to 28 day mortality, nor was there any early improvement in haemodynamic state or organ function. A systematic review published in 2014 again did not find any benefit in outcome.

The findings of these studies, together with the adverse effects of HVHF (excessive clearance of electrolytes, drugs and nutrients as well as cost – financial and nursing time) mean that HVHF cannot be recommended as standard practice for patients with septic shock and AKI.

Choice of therapy on the Intensive Care Unit

ICU patients can (broadly) be categorised into 4 groups when it comes to renal replacement therapy, although patients can move between categories during their illness.

Group 1: The critically ill patient with multi organ failure – CVVH 35mls/kg/hour

CVVH is effective in clearing solutes and acid load and it could be said that it more closely mimics the kidney. In the critically ill patient first presenting to the ICU with renal failure needing RRT, it is important to ensure that adequate therapy is delivered. Given that in the first couple of days there may be periods of filter down time to accommodate diagnostic or therapeutic procedures, prescribing 35mls/kg/hour will hopefully ensure that 20-25mls/kg/hour (as per the current evidence) is delivered.

Group 2: Recovering multi organ failure OR AKI with high solutes initially – CVVH 25mls/kg/hour
After 48-72 hours the patient should be reassessed. If they have resolving multi organ failure but still an ongoing need for RRT then CVVH can be reduced to 25mls/kg/hour. This assumes that solute control and acid base balance are adequate.

For patients who present with a high urea (> 25-30mmol/l) as part of an AKI, then a lower rate of effluent production rate should be used to avoid rapid osmotic shifts. In extreme cases, rapid osmolar changes can cause a shift of fluid into brain cells causing cerebral oedema, a condition called *disequilibrium syndrome*. It can manifest as drowsiness, headache, fits and even coma. These signs are not easily seen in sedated ventilated ICU patients. Therefore the urea level should be brought down by no more than ⅓ in a 24 hour period when renal replacement therapy is first being started. This scenario is analogous to slowly bringing down the glucose in someone with diabetic ketoacidosis. This principle should also be applied to patients who are known to have end stage renal failure but who have not yet started regular haemodialysis.

If there are excessive periods of down time then an effluent production rate should be considered to compensate for this.

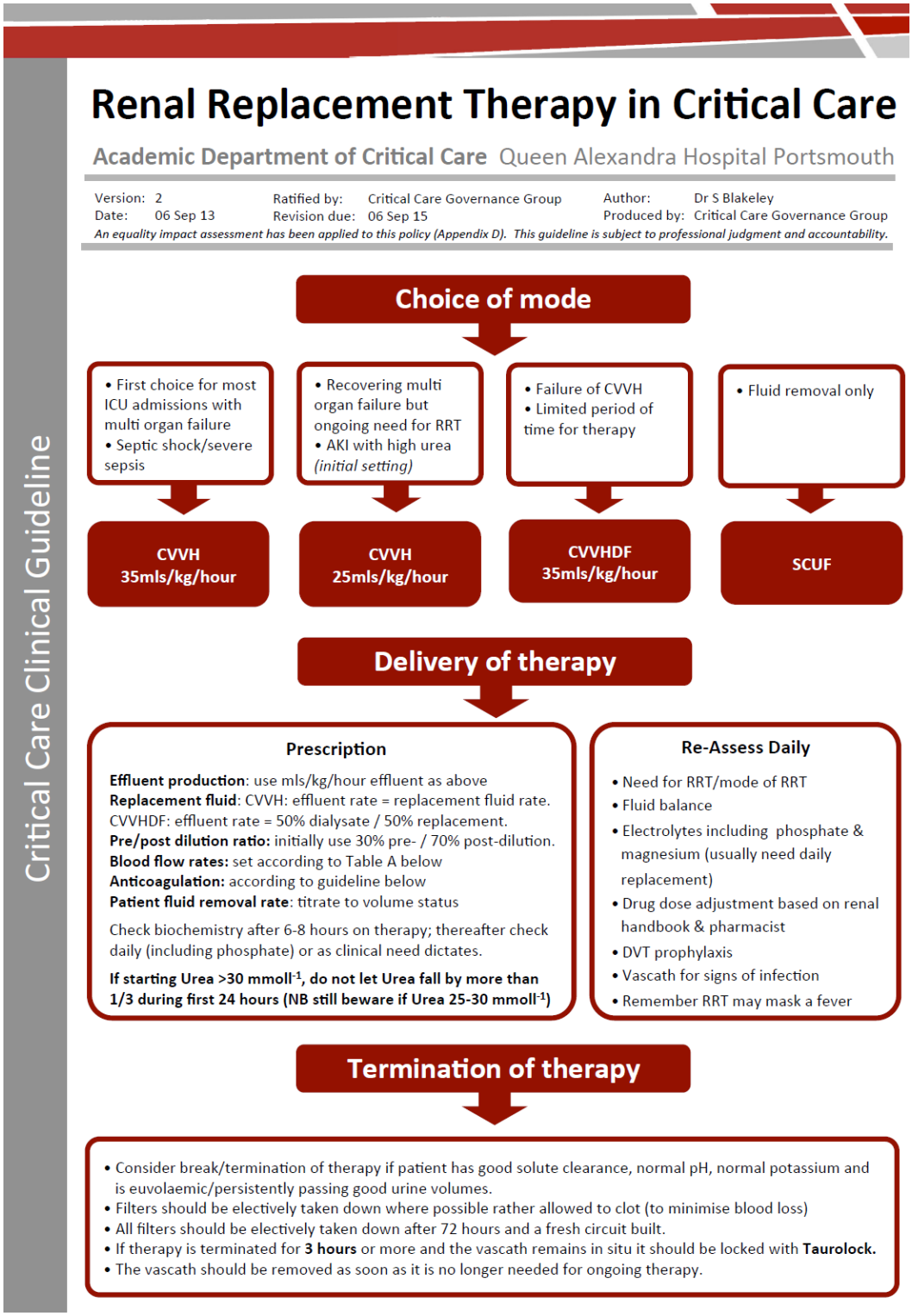
Group 3: Failure to clear acidosis or solutes on CVVH – CVVHDF 35mls/kg/hour
Some patients have a profound metabolic (often lactic) acidosis and CVVH may not correct the acidaemia in the time scale required and it is important to deliver effective therapy up front. They should be started on CVVHDF 35mls/kg/hour.

Some patients, such as those with end stage renal failure who are usually on maintenance haemodialysis or peritoneal dialysis may have high solute levels (which may be usual for them). A 4 hour haemodialysis would clear these well but continuous therapies take longer. There may therefore be a clinical need to change to CVVHDF to clear solutes quicker (e.g. to fit in with theatre times).

Group 4: Fluid removal only - SCUF
Some patients may need RRT predominately for fluid removal. They may well have been on RRT for a few days and their pH, potassium level and urea may be acceptable, what they need is just fluid removal. If this is the case then the machine should be set just to remove fluid, this can be done in either SCUF mode or in CVVH with no replacement fluid infused.

Figure 10: Summary of which therapy to use when (also refer to text)

Please refer to full guideline available via the departmental website



Equipment for continuous renal replacement therapy

There are several components that go into making up a complete haemofiltration circuit.

1. Haemofiltration machine
2. Vascular access
3. Haemofilter and blood tubing
4. Replacement fluid or dialysate fluid

1. Haemofiltration machine

There are several types of haemofiltration machine on the market. Most modern machines now provide all the standard therapies, CVVH, CVVHD, CVVHDF, SCUF and therapeutic plasma exchange (TPE) with higher blood pump speeds and higher rates of effluent production to cope with current best practice guidelines. On the DCCQ we use the Prismaflex machine.

2. Vascular access

When continuous renal replacement therapy was first designed (by Dr Kramer in 1977), one cannula was placed in the femoral artery and one cannula in the femoral vein. Blood came out through the arterial cannula (red for artery) with the patient's own cardiac output driving the blood through the circuit. Blood was returned to the patient via the venous line (blue for venous). This design was called *arterio-venous*; CAVH for example would have been continuous arterio-venous haemofiltration. Technology then developed with vascular access now being a single duel lumen cannula inserted into a central vein. Arterio-venous renal replacement therapy is very rarely used, and almost all CRRT is now veno-venous.

The two lumens are either side by side (double D, parallel) or one within the other (co-axial). Blood is pumped out of the patient through holes in the side of the catheter into the outer lumen and then returned to the patient through the inner lumen which has a hole at the very tip. Tradition continues and the 'out' side is still called arterial or access (red) and the 'return' side is still called venous (blue). Dialysis catheters (vascaths) are wide bore (generally 11.5-13.5 French) to allow adequate pump speeds and are made of biocompatible material.

Insertion of dialysis catheter

The vascath should always be inserted in an aseptic manner. Often ICU patients already have lines in place and there may be certain reasons why you cannot put a line in one particular place.

- *Femoral vein*: This is often easy to get to, gives good flows and is safe if the patient has a bleeding tendency. However they may be problematic in patients with large abdomens, with high intra abdominal pressure and in patients who are more mobile. There are mixed views as to whether there is an increased infection risk with femoral lines but this does not seem to be seen in our practice.

- *Internal jugular vein*: If using the jugular approach then the right internal jugular often gives better flows than the left as the route to the junction of the right atrium and superior vena cava (where the tip should sit) is more direct.

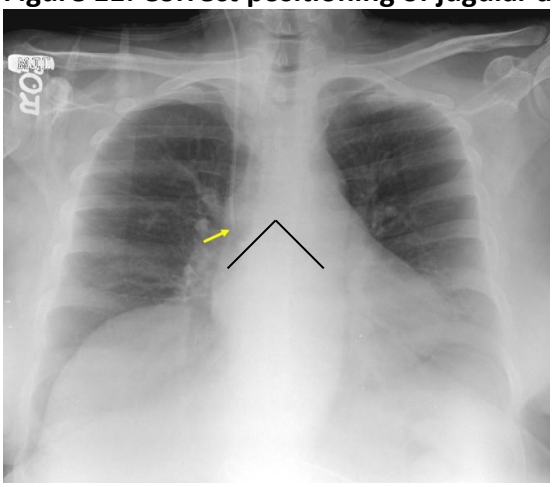
- *Subclavian vein*: The subclavian approach is often avoided or left till the end as there are concerns about inserting subclavian lines in patients who are coagulopathic. Subclavian lines should also be avoided if at all possible in patients who are likely to need ongoing renal replacement therapy. Subclavian dialysis lines are associated with the development of subclavian stenosis which can cause problems later on if the patient were to need an arterio-venous fistula forming (for chronic dialysis).

Correct positioning of the vascath

- For femoral lines the tip of the line should sit at the junction of the inferior vena cava and therefore should be a minimum of 20cm long.

- For neck lines (i.e. jugular and subclavian lines) the tip should sit at the junction of the superior vena cava and right atrium (see figure 11). For right sided lines a 15cm line is generally sufficient, but for the left sided approaches a 20cm line is sometimes needed depending on the size of the patient. The tip should not lie within the right atrium as there is a risk of perforation of the wall. With tunnelled long term dialysis catheters the tip lies in the right atrium, but this is acceptable because long term catheters are made of softer material which does not cause erosion. Tunnelled lines are not generally used on the ICU though.

Figure 11: Correct positioning of jugular and subclavian lines



When correctly positioned the tip of the catheter lies at the cavo-atrial junction, just above the level of the inferior border of the right main stem bronchus.

If the line is not correctly positioned on the CXR it should be repositioned before use.

Both the insertion and any repositioning should be documented in the patient notes.

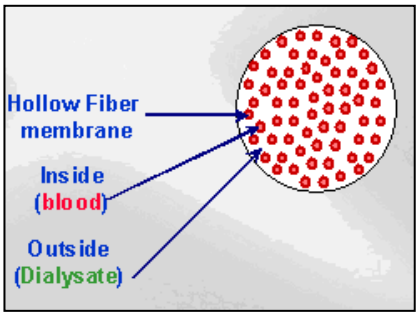
Care of the vascath

- It should be inserted in a fully aseptic way, as with any other central venous catheter.
- The catheter should only be used for dialysis, except in an emergency where it may be the only vascular access and following direction from the senior doctor on duty.
- It is important whenever handling the line to follow the departmental guidelines to reduce the risk of introducing infection.
- When the dialysis line is not in use it should be 'locked' with TauroLock™ solution to prevent the formation of blood clots within the line. Refer to DCCQ guideline.

It is vitally important that the line is inserted in a fully aseptic way, and that the blood flows are checked before the person inserting it walks away. A poorly functioning line leads to poorly functioning dialysis.

3. The haemofilter

Figure 12. Haemofilter structure



The haemofilter (filter) is composed of thousands of hollow fibres all bundled together in a cylindrical case (figure 12). Blood enters one end of the tube and then passes through the centre of the hollow fibres before exiting at the other end. This design significantly increases the surface area across which solutes can move. The filter size is described in terms of 'square metres' (about 0.6-1.5m^2). The fibre material is a semi permeable membrane across which solute clearance can take place.

The fibres can be made of either a cellulose based material or a synthetic material. Different filter types have different characteristics with respect to biocompatibility, size and number of the pores (surface area), how well it lets solutes through (sieving coefficient) and how well it lets water through (flux).

Cellulose vs. synthetic fibres

Cellulose or modified cellulose fibres (e.g. cuprophane, cellulose acetate) tend to be hydrophilic and low flux. Being hydrophilic means that the membrane soaks up water; this provides an ideal environment for diffusion. Synthetic fibres (e.g. polysulphone, polyacrylonitrile and polyamide) are hydrophobic and high flux with high sieving coefficients for a wide range of solutes; this makes them idea for convective therapy. Synthetic fibres are traditionally more biocompatible than cellulose fibres.

Membrane biocompatibility

When blood comes into contact with the blood tubing and the filter (foreign substances) there is a degree of complement and leucocyte activation. In other words a degree of inflammation is triggered. Substances that cause more of an inflammatory reaction are termed bio*in*compatible and those that cause less, bio*com*patible. This inflammatory activation was thought to have an adverse effect on the patient and therefore more biocompatible synthetic membranes were developed. Historically cellulose filters were associated with more bioincompatibility but there is no strong evidence now to suggest that the newer (modified) cellulose membranes are any worse than the synthetic membranes in terms of patient outcome.

Membrane flux

Flux is the degree of water removal and therefore convective transport across the filter. It is dependant on the size of the pores in the membrane and the fibre characteristics. High flux membranes have a larger pore size and therefore a high permeability coefficient to water. This is

needed if convective therapy is to be used as this involves the removal of large volumes of plasma water. Most membranes used on the ICU are high flux synthetic membranes.

The sieving coefficient

This describes how permeable the membrane is to solutes during ultrafiltration. The bigger the solute then the less easily it passes through the membrane. The sieving coefficient is the ratio of the concentration of the solute appearing in the effluent (ultrafiltrate) compared to the concentration of the solute in the blood (or more accurately plasma water). In other words a sieving coefficient of 1 (for example urea) means *complete* permeability, and a value of 0 (for example albumin) means *no* permeability.

Clearance by convection is determined by the filtration rate and sieving coefficient.

Clearance (mls/min) = ultrafiltration rate x sieving coefficient
So for example: for urea (sieving coefficient of 1) at an ultrafiltration rate of 35mls/kg in a 70kg patient the clearance of urea is 2450 mls/hour [1 x 35 x 70] or 40mls/min.

Other terms used:

Transmembrane pressure (TMP)

The pressure of the blood within the hollow fibres is positive and can be made more positive by increasing the speed of the blood going through the extracorporeal circuit. Outside the hollow fibres is a 'space' that is either filled with dialysis fluid (going in the opposite direction) or plasma water (ultrafiltrate) being removed from the patient by the effluent pump. This outside pressure can be made lower (i.e. more negative) by increasing the fluid removal rate or increasing the replacement flow rate. The transmembrane pressure is the pressure exerted on the haemofilter membrane and is the difference between the blood and fluid compartments just described.

$$\text{Transmembrane pressure} = \frac{(\text{filter pressure} + \text{return pressure})}{2} - \text{effluent pressure}$$

Filter drop pressure

This is an indication of the pressure in the hollow fibres of the haemofilter from where blood enters the filter to where blood comes out. If the fibres become clotted, even with just small amounts of clot (micro clotting) then the pressure starts to rise. It can often be an early sign that the filter is starting to clot.

Adsorption

Some larger solutes are able to stick to the surface of the membrane; different membranes have different adsorptive properties. This phenomenon has been explored when it comes to inflammatory mediators such as cytokines. It has been shown that in the first couple of hours the filter becomes saturated with proteins; they are simply too big to pass through the filter.

4. Replacement and dialysate fluid

Although used differently, 'replacement fluid' and 'dialysate fluid' are the same composition and are often just called 'haemofiltration fluid' as a whole.

Replacement fluid is a sterile, balanced electrolyte solution that essentially contains sodium chloride, varying concentrations of electrolytes (potassium, calcium, magnesium), varying concentration of glucose and a buffer (lactate or bicarbonate) (Table 12). The buffer that is most commonly used now is bicarbonate. Any lactate that appears in bags of replacement fluid is there to maintain neutrality rather than act as a buffer.

Table 12: Composition of commonly used fluids on the ICU

	Hemosol BO (Gambro)	Prismasol4 (Gambro)	*Hartmann's solution*
Sodium	140 mmol/l	140 mmol/l	*131 mmol/l*
Potassium	0 mmol/l	4 mmol/l	*5 mmol/l*
Calcium	1.75 mmol/l	1.75 mmol/l	*2 mmol/l*
Magnesium	0.5 mmol/l	0.5 mmol/l	*0 mmol/l*
Chloride	109.5 mmol/l	113.5 mmol/l	*111 mmol/l*
Bicarbonate	32 mmol/l	32 mmol/l	*0 mmol/l*
Glucose	6.1 mmol/l	6.1 mmol/l	*0 mmol/l*
Lactate	3 mmol/l	3 mmol/l	*29 mmol/l*
Osmolarity	287	301	*278 mmol/l*
pH	7.0-8.5	7.0-8.5	*6*
Bag size	5000 mls	5000 mls	*500-1000 mls*

Pre and post dilution

As already mentioned, replacement fluid can be given before the filter (pre dilution) or after the filter (post dilution) or in combination (Figure 13).

There are some important differences between pre and post dilution.

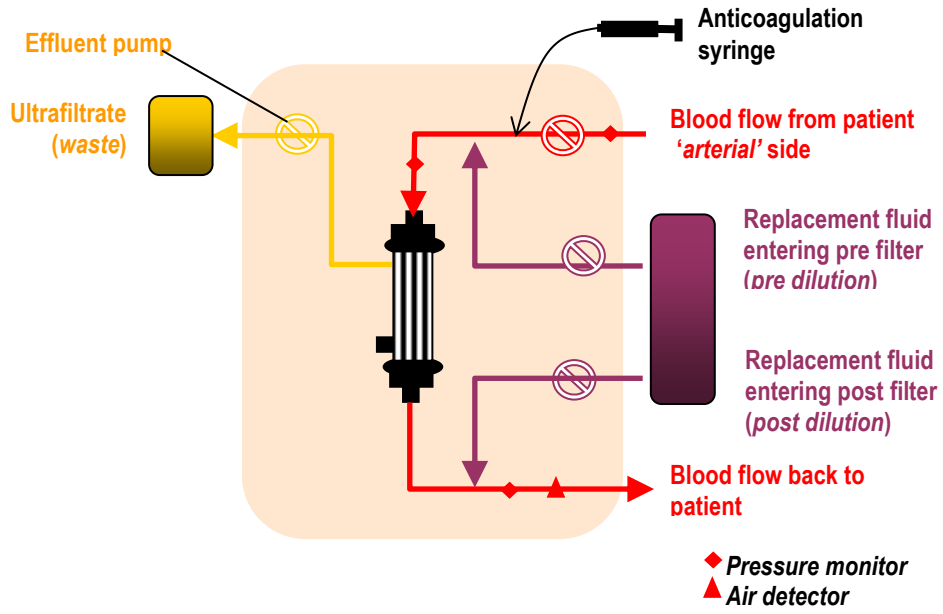
- As blood enters the filter and plasma water is removed (by the process of convection), blood starts to concentrate through the length of the haemofilter. If the replacement fluid is infused pre filter, in other words before plasma water is removed, then this dilutes the blood and so reduces the degree of haemoconcentration that could occur. This can be used as an adjunct to anticoagulation/no anticoagulation during CRRT.

- On the down side, by diluting the blood before it goes into the haemofilter solute clearance is reduced. Only a certain 'fraction' of the plasma is cleared of plasma water (and therefore of solutes) each time it goes through the filter. If the blood is diluted before this plasma water is removed the solutes will be dissolved in a larger volume but still only the same fraction of water will be removed – containing less solute. Depending on the amount of plasma water being removed (the ultrafiltration rate) there will be a variable reduction in solute clearance with pre dilution as compared to post dilution. For example, at

ultrafiltration rates of 2000mls/hour, then urea clearance is reduced by 15% with pre dilution compared to post.

Using a combination of pre and post dilution simultaneously maximises the benefits of pre dilution on filter life but at the same time maintains the benefits of post dilution on solute clearance. The most commonly used split between pre and post dilution is 30% (pre) to 70% (post). If there are problems with filter survival time and clotting then the percentage of pre dilution can be increased (e.g. to 50:50).

Figure 13: CVVH circuit showing both pre and post dilution



Anticoagulation on renal replacement therapy

As blood comes into contact with the tubing and the haemofilter there is activation of the coagulation cascade (both intrinsic and extrinsic pathways) and therefore the risk of clotting within the filter. Low levels of filter clotting can lead to a poorly functioning filter and ultimately can lead to the whole filter clotting. Recurrent clotting of the filter and circuit is not only a drain on resources (both financial and nursing) but the patient loses the blood that may still be in the system and ends up with inadequate solute clearance. The majority of filter problems can be traced back to the vascular access, inappropriate blood flows or excessive haemoconcentration within the haemofilter rather than *only* due to ineffective anticoagulation. The risk of bleeding needs to be balanced against the disadvantages of a filter clotting. It is always better to lose a filter rather than lose a patient to major haemorrhage.

Refer to the DCCQ guidelines on anticoagulation for renal replacement therapy.

No anticoagulation

Many critically ill patients have a degree of coagulopathy (e.g. elevated INR or APTR), may be thrombocytopenia or are at high risk of bleeding for other reasons (e.g. post major surgery). In these patients there is often no need to actively anticoagulate the circuit. The only point to remember is that abnormal coagulation may be a reflection of a consumptive coagulopathy and some form of anticoagulation may need to be considered if filter survival time is in adequate.

Anticoagulation free therapy has been successfully used by many units including our own with acceptable filter life spans. Looking at the 2 most recent dose studies (ATN 2008 and RENAL 2009), 46-60% of patients needing CRRT had no anticoagulation used. For successful anticoagulation free therapy there should good vascular access and appropriate pump speeds. A greater percentage of pre dilution may need to be considered to reduce blood viscosity or considering a diffusive treatment.

Unfractionated heparin

In critically ill patients who have a normal or near normal coagulation profile, some form of anticoagulation is generally needed. The commonest anticoagulant used is unfractionated heparin (UFH). Heparin is cheap and familiar to everyone. It acts by increasing the action of antithrombin in the coagulation cascade and inhibits factors Xa and IIa. If there are low levels of antithrombin III as seen in some critically ill patients then heparin may not work as well.

The circuit is usually primed with heparinised saline before starting as heparin is very 'sticky' and coats the plastic tubing and the haemofilter surfaces. Some units use a bolus dose of heparin prior to starting; however on our unit a bolus is not part of the protocol. An infusion of low dose heparin is run; 5-10 IU/kg per hour. The APTR should be checked regularly, not to make sure that a target APTR is reached, more to ensure that the APTR is *not* too high. The aim is to have a filter that is running well and keep the APTR 1.4 or less. This is to try to minimise the risk of bleeding but also because it has been shown that there is not a linear relationship between the APTR levels and

how long the filter lasts for. In the event of bleeding due to too much drug, heparin can be neutralised by protamine.

Heparin is associated with the development of heparin induced thrombocytopenia (HIT). This is an immune mediated reaction to heparin with the formation of heparin antibodies and a rapid and significant fall in the platelet count. It can be associated with the development of thromboses. Recurrent clotting of the filter *for no good reason* associated with *marked thrombocytopenia* should raise the suspicion of HIT.

Low molecular weight heparin

Low molecular weight heparins (LMWH) such as enoxaparin can also be used. They work by inhibiting factor Xa and are monitored through anti-Xa levels rather than APTR. LMWHs are not neutralised by protamine so in the case of bleeding due to the drug, fresh frozen plasma should be given. LMWHs are associated with a lower risk of HIT but it can still occur.

Unfractionated heparin versus low molecular weight heparin
Some groups have found better filter survival time with LMWH but the evidence is not overwhelming. UFH is cheap, familiar to all, can be monitored by the APTR and can be neutralised in the event of an overdose. UFH is the standard for CRRT on the DCCQ.

Prostacyclin

Prostaglandin I_2 (prostacyclin, flolan) inhibits platelets aggregation and can be used as a form of anticoagulant during CRRT. It is often used in patients who have a high risk of bleeding but need some form of anticoagulant over the filter, however its popularity is waning. Prostaglandins have vasodilatory effects and at higher doses can cause hypotension; therefore low doses of 2-5 ng/kg/minute are used.

Regional citrate anticoagulation (RCA)

Calcium is needed as a co factor in the clotting cascade and therefore low calcium levels inhibit coagulation. Citrate chelates (binds) calcium so reducing ionised calcium levels and thereby inhibiting clotting. If sodium citrate is infused into the arterial limb of the extracorporeal circuit (before the filter) then the blood is effectively anticoagulated as it goes through the filter. After the blood leaves the filter calcium is re-infused to maintain systemic calcium levels (to account for calcium loss through the extracorporeal circuit). This is an effective way of anticoagulating *just* the filter rather than the patient as a whole. There needs to be very close monitoring of the calcium levels with appropriate replacement otherwise the patient may become profoundly hypo or hypercalcaemic. Citrate is removed by the extracorporeal circuit, and any entering the systemic circulation is metabolised to bicarbonate by the liver, kidney and muscle and as a consequence a metabolic alkalosis may develop. Trisodium citrate solutions also contain a substantial amount of sodium and patients may become hypernatraemic. Finally there is the potential that if an excess amount of citrate enters the circulation this could lead to citrate toxicity with a severe metabolic acidosis.

RCA versus heparin

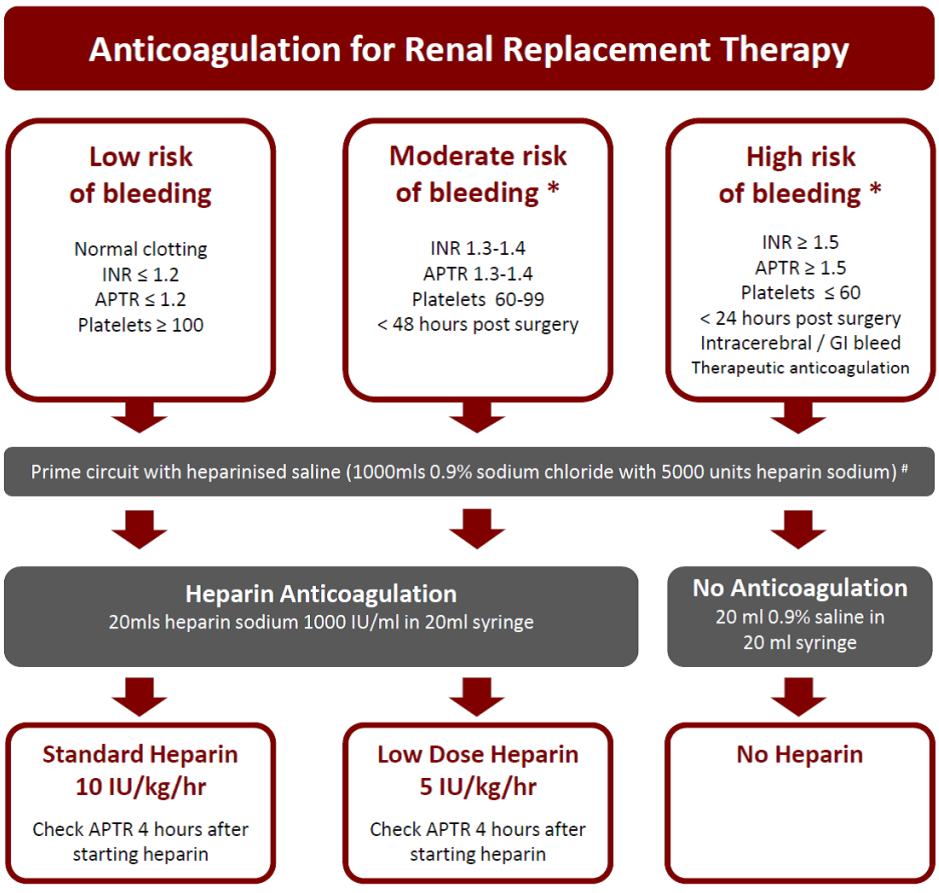
Regional citrate anticoagulation (RCA) has been shown to be a very good way of anticoagulating the extracorporeal circuit but its use had previously been limited as it can be quite time consuming, needs a strict protocol and has the potential to cause metabolic upset. It has however become more widespread and is gaining popularity. Well used protocols are in place, suitable bags of replacement fluid are available and new haemofiltration machines have the capability for RCA by linking together all flow rates so making therapy easier and safer to deliver.

Studies that have been done show a superior filter survival time when compared to heparin with less spontaneous filter failure. It has also been recommended for use in patients at high risk of bleeding, although it is worth mentioning that patients at high risk of bleeding were actually excluded from the main citrate versus heparin randomised controlled trials.

Other forms of anticoagulation

There are a range of other types of anticoagulant available but there is not extensive experience in using them on CRRT. They include danaparoid (a heparinoid substance) which is often used in patients who develop HITS, fondaparinux (an indirect thrombin inhibitor) and recombinant hirudins (direct thrombin inhibitors).

Table 13: Choice of anticoagulation therapy on the DCCQ (please refer to intranet for full guideline)



Complications associated with renal replacement therapy

CRRT is an invasive process and there is the potential for a number of complications to develop. It is important to know of these complications in order to prevent them or promptly recognise and treat them.

Hypothermia

There is a significant cooling effect as the patient's blood is circulated round the extracorporeal circuit and large quantities of room temperature replacement and dialysate fluid are used. This may be advantageous in some cases, but for others this could lead to hypothermia. Warming devices are available that warm the blood or warm the replacement fluid. It is important to remember that the filter may mask a fever and therefore there should be regular microbiological surveillance while the patient is on the filter. Beware the rebound pyrexia when the patient comes off the filter.

Hypotension

Hypotension can occur for a number of reasons during therapy.

- Excessive or too rapid fluid removal can cause hypotension. If the patient is intravascularly deplete then filling should be considered. If however they are overloaded then consider slowing down or stopping fluid removal, at least temporarily. The fluid may be 'in the wrong place' and may need time to equilibrate.
- Often renal replacement therapy is being provided to patients who are already very unwell and may be on vasopressors for hypotension. Hypotension on the filter may be a reflection of their underlying illness.
- Other causes of hypotension should always be excluded before blaming the filter. For example myocardial infarction, new sepsis and cardiac arrhythmias precipitated by electrolyte disturbances (CRRT can lead to excessive potassium and magnesium removal).
- Occasionally patients can have reactions with the haemofilter leading to the release of inflammatory mediators. This is uncommon with new filters but has been reported with the AN69 filter in patients who are on (or have been recently taking) angiotensin converting enzyme inhibitors (ACEIs). This is due to the release of bradykinin due to the negatively charged membrane and the reduction in bradykinin breakdown due to ACE inhibition. In these patients an alternative membrane should be used.
- Finally there are some patients who become hypotensive when starting CRRT for reasons that are not fully understood and who do not tolerate ideal blood flow rates – they are very difficult to manage.

Related to vascular access

The same care should be taken with dialysis catheters as is taken with any other central venous catheter in order to prevent catheter related blood stream infections. Vessel thrombosis can also occur associated with dialysis catheters in which case the line should be removed.

The same principles of care as with any central venous catheter should be applied to dialysis catheters. See DCCQ guideline Care of Dialysis Catheters.

Electrolyte and phosphate imbalances

Potassium. The filter is very effective at removing potassium and indeed this may be the goal of therapy. Once any excess potassium is removed it is often necessary to add potassium to the bags of haemofiltration fluid to keep plasma levels within normal limits.

Sodium. The sodium concentration of replacement fluid is 140mmol/l (on average) and infusing large quantities of replacement fluid or having circulating dialysate fluid can lead to alterations in the patients plasma sodium. This should be carefully considered when patients are very hyponatraemic as this may lead to a (too) rapid correction of their sodium. Further information on how to manage these patients is available via the intranet.

Magnesium. The filter removes magnesium and this may need to be supplemented, especially if the patient has cardiac arrhythmias.

Phosphate. A functioning filter is very good at removing phosphate and phosphate depletion should be treated promptly. On average once the filter is running well, at least 1 phosphate polyfuser will be needed per 24 hours.

Blood loss

This can occur in a number of ways:

1. If the filter clots before the blood can be returned the patient, then this volume of blood is lost – around 150mls. If the filter recurrently clots then this volume can soon add up.
2. Over anticoagulation on the filter can lead to bleeding around the entry site of the vascath, from other puncture sites or even intra abdominal or intracranial bleeding.
3. Critically ill patients are often coagulopathic or at risk of bleeding, as are patients with advanced renal failure. The exact cause is not known but is felt to be multifactorial, but one reason is due to abnormal platelet function – not their number, but how well they stick together.

The following can be done to reduce the risk of bleeding:

1. Ensure the filter is kept running. Electively take it down rather than wait for it to clot.
2. Follow anticoagulation guidelines and check coagulation as recommended.
3. The risk of GI bleeding should be addressed with gastro-protection (ranitidine is fine unless there is a history of peptic ulcer/reflux disease in which case a proton pump inhibitor should be used) and early feeding – as with all ICU patients.
4. DDAVP (desmopressin – 0.3 mcg/kg in 50mls saline over 30 mins) can be used to treat uraemic ooze. Active surgical bleeding should be treated surgically, but DDAVP can be considered as a pre op adjunct in someone who has very high levels of urea. The mechanism of action is not fully clear, but one proposed action is that it acts by increasing the release of factor VIII and enhancing the expression of von Willebrand factor.

5. Cryoprecipitate is rich in factor VIII, von Willebrand factor and fibrinogen and may be considered after DDAVP if bleeding still continues, in the setting of a normal INR/APTR – these should always be corrected first.

Air embolus

Making sure all the connections are tight and that alarms are acted upon promptly should prevent this uncommon, but life threatening complication of CRRT. The signs of an air embolus may be non specific in sedated, ventilated critically ill patients, but may be seen as unexplained hypotension. If this happens the patient should be put onto their left lateral position, 100% oxygen given and senior help called for immediately.

Termination of therapy

In a certain number of patients, therapy may be stopped as part of withdrawal of therapy and a move to comfort care rather than full active treatment. Some patients may have 'filter holidays' if they have adequate solute clearance, normal acid base balance and are euvolaemic. This may give 'plastic free time' or an opportunity to reassess the clinical state. For others, termination of therapy occurs when there is return of intrinsic renal function or possible return of renal function. True assessment of renal function while on CRRT is hard. Urea and creatinine give an indication of solute clearance by the filter not the patient's own renal function (don't confuse a working filter with the kidneys getting better). Urine output has been used, and although it has many limitations it is not a bad indicator that the kidneys are starting to do something – the return of salty water clearance may be followed by proper solute clearance.

The use of biomarkers may be the way forward but work is still ongoing to determine which biomarker is the best in determining return of renal function in critically ill patients.

Care of the patient while on renal replacement therapy

Nutrition

Acute kidney injury is associated with an increased basal metabolic rate and number of nutritional problems; these may be aggravated by the process of haemofiltration.

- There is marked protein catabolism leading to negative protein balance leading to a loss of lean body weight. Amino acids can be lost across the haemofilter, and can be over 10-15g/day. Impaired glucose utilisation and insulin resistance together with increased hepatic gluconeogenesis and reduced glycogen synthesis in muscles leads to hyperglycaemia and so glucose should be controlled as with any other critically ill patient
- Hypertriglyceridaemia and low HDL cholesterol levels occur due to a defect in lipolysis.
- Levels of certain vitamins and trace elements (e.g. selenium) are usually low in patients with AKI. Some water soluble vitamins and certain anti oxidants can also be lost across the filter and again work continues as to the benefits of extra supplementation.

It is therefore very important that patients with on CRRT (and indeed those with renal failure) are fed. Many chronic renal failure patients are on a low protein diet but there is no role for this in critically ill patients with an acute kidney injury. Patients should receive 20-35 kcal/kg/day as with other critically ill patients.

Fluid balance

If a patient is significantly overloaded and fluid is being removed on the filter, it is sensible to try and reduce the hourly or daily intake of fluid to the patient. Examples include changing antibiotics or other drugs to oral and as mentioned above, changing the feed to a concentrated (2 Kcal/ml) feed. Fluid restriction should continue when patients are not on the filter but remain oliguric or anuric. Feed should never be sacrificed to help with fluid balance. Always remember SCUF.

Appropriate drug dosing

Drug kinetics are slightly different depending on whether the patient is on a predominately convective therapy (e.g. CVVH) or a diffusive therapy (e.g. CVVHD). Drugs with a low molecular weight are cleared the same, but drugs with a larger molecular weight are cleared better with convection. Water soluble drugs are removed efficiently but protein bound drugs may not be removed at all. As discussed before, the sieving coefficient is a measure of how easily a solute passes through the haemofilter membrane. Albumin has a sieving coefficient of 0, so none of it passes through the membrane. Therefore any drugs that are bound to albumin will also not pass through the membrane.

There is a risk that patients may be under or over dosed while on the filter which may have important clinical ramifications. The best way to confirm that the patient is getting the right dose of drug while on CRRT is to measure drugs levels. If this is not possible then advice should be taken from an ICU pharmacist or by referring to a specialised renal drug hand book (there should always be one available on the ICU). There is a great deal of information now available from lab studies to guide us with the right dosing.

Infection control

As already mentioned the presence of a central venous dialysis catheter is a portal of entry for micro-organisms and close attention should be paid to the dialysis catheter. The dialysis catheter should be removed if there is any sign of infection.

Uraemia itself is associated with a reduced total lymphocyte count and delayed cutaneous sensitivity to skin test antigens, in other words patients with renal failure have a degree of immunosuppression. This does not however mean that renal failure patients need prophylactic antibiotics.

Due to its cooling effect CRRT can mask a fever. A fever despite being on the filter is very significant, cultures should be taken and the source looked for. However, the absence of a fever while on the filter does not imply that there is no infection, so a high index of suspicion should be

maintained and inflammatory marked watched. A patient on the filter is never apyrexial – they are 'apyrexial *on the filter*'.

Nursing care of the patient on renal replacement therapy

This should continue as usual with close observation for the development of complications as listed above. Moving the patient and physiotherapy may 'make the filter alarm' but is not a reason not to provide this care. The presence of femoral lines may hinder the patient sitting out, if this is the case, where possible the line should be changed to a neck line. Refer to table 14.

Monitoring of laboratory tests

Once the haemofilter is up and running certain biochemical and haematological tests need to be performed as shown in table 15.

Table 14. Daily check list for patient care while on the haemofilter

System	Assessment	Comments
Renal/fluid balance	* Assess need for therapy each day * Determine what procedures/transfers are due that day * Assess fluid balance status – clinically and on paper * Assess need for fluid removal or administration * Consider need for RRT if patient passing good volumes of urine * Assess need for a urinary catheter	• Based on up to date clinical, biochemical and acid-base parameters • Make sure RRT fits around procedures (or the procedure fits around RRT) • If fluid needs to be removed, can the daily intake be reduced? E.g. stop excess maintenance fluid, change iv drugs to oral • If passing urine, is the volume enough to consider a trial off RRT? • If anuric, do they need a urinary catheter still?
Cardiovascular	* As per usual daily assessment * Reassess changes in haemodynamic instability while on RRT	• Any haemodynamic instability should be assessed fully rather than blaming RRT • Reassess fluid balance state, development of new sepsis, myocardial infarction etc.
Respiratory	* As per usual daily assessment * Reassess changes in oxygenation while on RRT	•Worsening oxygenation could be an indication of fluid over load • Reassess fluid balance status
Nutrition and metabolic	* As per usual daily assessment * Ensure the patient is being fed appropriately * Ensure potassium and phosphate are kept within normal ranges	• Does the feed need to be a concentrated feed to help with fluid balance?
Neurological	* As per usual daily assessment * Assess dose/method of sedation is appropriate for renal failure	• Are the drugs for sedation starting to accumulate due to the patient's renal failure? • Does the patient need a sedation break or reassessment of sedation?
Temperature and infection control	* Aim for normothermia (unless clinically indicated otherwise) * Ensure all infection control measures are followed * Determine date of insertion of vascath * Actively check for presence of any possible line infection	• The circuit blood warming device and/or surface warming may be needed • Could the filter be masking a fever? • Ensure blood cultures taken if concerns regarding infection • If the vascath a potential source of infection or is no longer needed – then remove
Musculoskeletal / integumentary	* As per usual assessment	• RRT should not stop regular re positioning and physiotherapy • If a femoral line is hindering mobilisation – can it be repositioned?
'Housekeeping'	* Review dosing of drugs according to patients renal function/RRT * Ensure vascath locked with Taurolock if not being used * Ensure patients have thromboprophylaxis prescribed * Ensure gastroprotection prescribed (at renal dose)	• Have all nephrotoxic drugs been stopped (where possible)? • Have drugs been readjusted if needed if the patient is OFF or ON the filter? • Refer to DCCQ guideline regarding Taurolock • Review thromboprophylaxis on and off the filter • Patients with renal failure may have an increased risk of gastric ulceration

Table 15: Laboratory tests required while patient is on renal replacement therapy

Test	Frequency	Rationale
Urea and creatinine	Daily * Note: If starting urea was > 25 mmol/l check level 12 hours after starting CRRT	Once a patient is on the filter, urea and creatinine do not give an indication of what the patient's intrinsic renal function is – they give an indication as to the degree of solute clearance (good or bad) The aim is not necessarily to have the urea and creatinine within normal limits – a urea < 15 mmol/l is good solute clearance
Sodium and potassium	Daily * Note: Na/K will be checked more frequently on arterial blood gases	Serum sodium should be monitored closely if it is very high or very low to start with Extremes of sodium may need reconsideration of the composition of the replacement/dialysate fluid – discuss with a senior Potassium may need to be supplemented as CRRT is very good at removing potassium
CRP	Daily	Given the risk of infections and the potential for the filter to mask a fever, a rising C reactive protein should raise concerns about infection
Magnesium	Daily *	Aim to keep magnesium within the normal range
Phosphate	Daily	CRRT is very good at removing phosphate Most patients on CRRT will need phosphate supplementation, often on a daily basis. Aim to keep phosphate within the normal range
Full blood count	Daily * Note: Hb will be checked more frequently on arterial blood gases	Recurrent filter clotting can lead to a drop in haemoglobin over time Platelet count should be monitored daily especially if the patient is on heparin Given the risk of infections and the potential for the filter to mask a fever, a rising white cell count should raise concerns about infection
Coagulation	Daily or 6 hours after starting CRRT if heparin is used or 6 hours after any change in heparin infusion	See the DCCQ anticoagulation guidelines If low dose heparin is used the aim is not to actively prolong the APTR but to keep the filter running. A prolonged APTR runs the risk of bleeding
Blood cultures	As clinically indicated	'Routine' surveillance cultures are not needed

* More frequently only if clinically indicated

Therapeutic plasma exchange

Terminology and uses

The terms plasma exchange and plasmapheresis are often used interchangeably. Apheresis is a general term meaning a component of blood is removed or separated. Therefore *leuco*pheresis is the removal of white cells, platelet apheresis is the removal of platelets and plasmapheresis is the removal of plasma. With *plasma*pheresis, if the removed plasma is replaced with albumin, fresh frozen plasma or saline, this is called plasma *exchange*. If this 'exchange of plasma' is to treat a condition, it is called 'therapeutic plasma exchange' (TPE).

The rationale behind TPE is that circulating substances such as toxins, autoantibodies, immune complexes and large proteins can accumulate in plasma (see table 16). Plasma is just a carrier medium within the body; it carries nutrients, waste products, proteins, drugs and so on. By exchanging a patient's plasma with 'clean' substitute plasma, these circulating substances will be removed. It doesn't stop the body from producing more of these substances so the underlying condition needs to be treated, generally by using immunosuppressive drugs.

Table 16: Examples of substances potentially removed by TPE

Pathologic substance	Disease associated with particular substance
Immunoglobulins	• Hyperviscosity syndrome • Waldenstrom's macroglobulinemia, multiple myeloma
Autoantibodies	• Myasthenia gravis • Anti glomerular basement membrane antibody disease • Systemic lupus erythematosus • Systemic vasculitis
Lipoproteins	• Hypercholesterolemia
Circulating immune complexes	• Immune complex glomerulonephritis • Systemic lupus erythematosus • Systemic vasculitis
Protein bound substances and toxins	• Thyroid storm • Amantia phalloides toxins

Examples of conditions seen on the ICU requiring TPE

- *Guillain-Barre syndrome.* There is good evidence for the use of TPE in patients with severe GBS (if unable to move from the bed or needing ventilation). It is most effective if started within the first 7 days.
- *Systemic vasculitis* (especially if with pulmonary haemorrhage).
- *Anti-glomerular basement membrane disease (Goodpasture's disease).*
- *Thrombotic thrombocytopenia purpura (TTP).* TPE has been recommended using fresh frozen plasma.

Methods of plasma exchange

Centrifugation machines spin the patient's blood to separate the different components whereas haemofiltration machines apply a transmembrane pressure which forces out plasma. A substitution fluid is then reinfused, the type determined by the condition being treated but is generally albumin, an albumin-saline mix or fresh frozen plasma. Often some form of anticoagulant is used (e.g. heparin) but the therapy can be performed without anticoagulation if there is a high risk of bleeding.

Main complications

Removing plasma not only removes the unwanted substances but also some of the wanted substances such as clotting factors, immunoglobulins and drugs. This can lead to an increased risk of bleeding (especially if some form of anticoagulant is used for the process) and an increased risk of infections (especially if immunosuppressant drugs are being given).
When FFP is being used there are complications associated with the FFP itself such as the risk of transmitted infections, fluid and salt overload and TRALI (transfusion related lung injury). Albumin is also a blood product and has the potential (but small) risk of transmitted infection.

Calculation of the TPE prescription

Exchanging one plasma volume will lower the plasma macromolecule levels by 60% and typically 1 to 1.5 times the plasma volume is changed each time. Blood volume is about 75ml/kg of body weight, but remember this blood volume is composed of cells as well as plasma. The plasma component can be calculated by subtracting the cell component (the haematocrit).

How do you calculate the plasma volume? (Assuming a 70kg patient with a haematocrit of 0.30)

Estimated blood volume = 70 ml x body weight (kg)
Total plasma volume = [1 – haematocrit] x estimated blood volume
Therefore for a 70kg patient the plasma volume would be 3430 mls [(1-0.30) x (70 x 70)]

The number of exchanges, exchange frequency and type of replacement fluid are detailed in the DCCQ guideline on plasma exchange.

End stage kidney disease

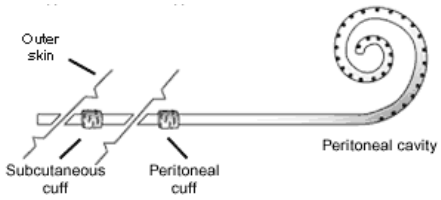
Introduction

At the end of 2012 (Renal Registry Data) there were 54,824 adults alive on renal replacement therapy with the median age of patients starting RRT being 58 years of age. Transplantation (RTx) is the most common treatment modality accounting for 50% of patients, haemodialysis (HD) in 43% and 7% on peritoneal dialysis (PD). When looking at survival of patients on renal replacement therapy, 50% of patients starting RRT aged 45-54 survived for more than 10 years, 50% of patients starting aged 55-64 survived for 5.75 years and 50% of patients starting RRT aged 65-74 survived for 3.3 years.

Peritoneal dialysis

Principles

Figure 14 A peritoneal Tenchoff catheter



This uses the patient's own peritoneal membrane as the dialysis membrane. The peritoneal membrane is a large membrane that lines the inside of the abdomen and covers the intra abdominal organs. It is made up of a thin layer of cells with blood vessels (capillaries) running through. Dialysis fluid is drained into the peritoneal cavity through a specialised peritoneal dialysis catheter (or Tenchoff catheter, see figure 14). This dialysis fluid contains a buffer (lactate or bicarbonate), glucose and electrolytes.

Blood running through the capillaries is high in urea, creatinine, potassium etc, therefore solutes moves from the capillaries, through the walls of the blood vessels, through the cells of the peritoneal membrane into the peritoneal cavity containing dialysate fluid. In other words solutes move from an area of high concentration to an area of low concentration through a semi permeable membrane – diffusion. The peritoneal dialysis fluid is allowed to sit in the abdomen for a period of time then it is drained out taking with it the waste solutes. Fresh dialysis fluid can be drained back in and the process repeated.

Glucose in PD fluid creates an osmotic gradient and so water moves out of the capillaries, through the peritoneal membrane and into the peritoneal cavity (ultrafiltration). Therefore when the fluid is drained out there *should* be more out than there was in. Different dialysis bags have different concentrations of glucose (1.36-4.25% glucose), a higher concentration of glucose leads to greater fluid removal. The bags are often colour coded to help the patient, or they call them weak, medium or heavy bags depending on the glucose concentration.

The PD fluid also contains a buffer (e.g. lactate, bicarbonate or a combination) this is to help correct the acidosis associated with chronic renal failure.

Methods

There are different ways of performing peritoneal dialysis, depending on how long the fluid stays in the abdomen for and whether it is done by hand or by a machine. The standard way is CAPD – continuous ambulatory peritoneal dialysis. Before a patient goes to bed they often drain in a bag of dialysis fluid and then when they wake up the next morning they drain out the old bag and drain in a new bag, this is called an exchange. They will do this again maybe 3 times during the day before going to bed again and leaving a bag in till the morning. Machines have been developed that do this all while the patient sleeps, except the exchanges are smaller and more rapid. This is called APD – automated peritoneal dialysis.

Complications

- *PD peritonitis* is defined as pain, cloudy bags, a white cell count of > 100 x 10^9 and a positive culture. The commonest organisms are coagulase negative *Staphylooccus* (30% cases) followed by *Staphylococcus aureus* and gram negative bacteria (e.g. coliforms – but not *Pseudomonas*). Treatment is with intraperitoneal antibiotics and there is a standard protocol which is followed till the infecting organism is known. Most of the time the infection clears, but in extreme cases a surgical wash out is needed and the PD catheter needs to be removed. Depending on the infection the patient may be able to have a new catheter inserted after a period of time, but in some cases a change to haemodialysis is needed.
- *Exit site infections* are usually skin organisms and may just cause local redness but may progress to severe cellulitis and peritonitis. Anybody handling the exit site needs to pay meticulous care to hand hygiene.
- *Failure of therapy*. The peritoneal membrane 'wears out' after a period of time. This is made worse by recurrent episodes of peritonitis, but the dialysis fluid itself can contribute to loss of efficiency of the peritoneal membrane. Glucose that is in the fluid gets broken down and forms compounds that can damage the membrane, this means that less ultrafiltration occurs and therefore bags with higher glucose in are needed, so making the problem worse. There are some newer types of fluid that are more protective of the PD membrane.
- *Hyperglycaemia* due to systemic absorption of glucose in the PD fluid.

Specific management of PD patients on the ICU

- PD exchanges should only be done by trained staff, the patient or trained family.
- The exit site should be dressed with whatever it is already dressed with. Clean the exit site only if needed, don't pick off any scabs or crusty bits unless they come off very easily.
- PD patients will know their up to date weight or have a record of it, they may or may not be on a fluid restriction as they may still pass urine.
- Depending on how well dialysed they are and what their clinical state is, they may be able to 'miss' a couple of exchanges rather than have to go straight on to haemofiltration.
- If PD cannot continue for whatever reason a temporary dialysis catheter should be inserted and the patient started on CRRT.
- Drug doses should be altered accordingly.
- Patients should be fed as with any other ICU patient; in the setting of a critical illness a low protein diet does not need to be stuck to.

In practice PD is rarely done on the ICU. Having an abdomen full of PD fluid may compromise ventilation. If they have had abdominal surgery with breach of the peritoneum then PD cannot be

performed so they would need to be converted to HD anyway. Finally PD exchanges would need to be performed by the renal nurses so practically this may be difficult. There have however been cases when PD has been run on the unit and if a patient has vascular access issues but a working PD catheter it makes sense to run PD.

Haemodialysis

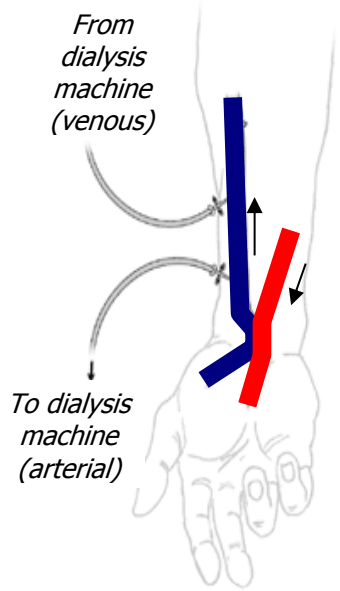
Principles

The principles of dialysis and diffusion have been discussed already. Intermittent haemodialysis uses different machines compared to those used on the ICU which give much higher blood flow rates (generally above 300mls/min). Instead of having pre made bags of dialysis fluid, ultrapure water is used to 'make' the dialysate from a concentrate. As the patient is exposed to large volumes of water (about 300l/week) it is vitally important that there are no water borne impurities (e.g. aluminium, bacteria or endotoxins). This makes water purity a big issue in chronic haemodialysis. Different methods, usually in combination are used to purify the water including reverse osmosis, filtration, activated carbon adsorption and ultraviolet irradiation. The water needs to be monitored regularly for quality.

Methods

HD sessions are on average for 4 hours, 3 times a week. When a patient presents acutely needing dialysis then a temporary dialysis line will be sited but ideally there should be planning leading up to a patient starting chronic dialysis with the formation of an arteriovenous fistula in advance. An arteriovenous fistula (AVF) is an arterialised expanded vein. For example, a radiocephalic fistula (figure 15) is the radial artery joined side by side with the cephalic vein at the wrist. A fistula takes about 6-8 weeks to 'mature' so that it is ready to use. Two needles can be inserted into the fistula, one outflow (arterial) and one inflow (venous). The fistula can be made of synthetic material such as PTFE.

Figure 15: A radiocephalic fistula



Specific management of HD patients on the ICU

- The fistula cannot be used while they are on the ICU, therefore if they need dialysis, a temporary dialysis line should be inserted and CRRT started. Where possible the vascath should not be the same side as the fistula or in the subclavian vein. The fistula or the fistula arm **should not be cannulated** (either arterial or venous). A non invasive blood pressure cuff or any other form of bandaging should not be used on the fistula arm.

- HD patients will know their up to date weight or have a record of it. More than likely they will be on a tight fluid restriction (often 1l per day) as they are often anuric if they have been on chronic HD for some time.
- As they will very rarely have any residual renal function extreme caution should be taken before giving potassium supplements or transfusing blood.
- Drug doses should be altered accordingly.
- Patients should be fed as with any other ICU patient; in the setting of a critical illness a low protein diet does not need to be stuck to.

Having said that the fistula cannot be used on the ICU, there have been times when CRRT has been run via needled fistulas. This is generally in the setting of very poor (or non existent) vascular access. If patient is sedated or very cooperative (so not moving) and high blood speeds are used it may be possible to run a modified CRRT session.

Some patients on IHD may have a tunnelled line in place (either as a bridge to fistula formation or due to lack of other access). This line can still be used for CRRT as long as it is not felt to be the source of their admission (i.e. sepsis). It should be treated in the same way as a normal vascath, particularly remembering to lock it afterward to prevent clotting. These lines cannot be just be 'pulled out' and there should always be a discussion with the renal team before removing it (it may be their last hope of access).

Renal transplantation (RTx)

During 2012, there were 2901 kidney (or kidney with another organ) transplants. Living donations account for 35.6% of all renal transplants, DCD kidneys account for 24.4% of transplants and DBD the remainder. This is a rise (in all groups) from the previous year. The 5 year survival of a cadaveric renal transplant is 84% (patient survival is 88%) and living donor kidney 96% (patient survival is 96%).

Immunosuppressive drugs

Patients receive a large amount of immunosuppression initially, which is then tailed off over a period of months to years, depending on the function of the kidney and the development of side effects. To start with they are often on triple therapy, usually prednisolone, Ciclosporin (Neoral) and azathioprine (AZA). In some cases tacrolimus is used in preference to ciclosporin, and mycofenolate mofetil (MMF) is used in preference to AZA.

It is vital that all the drugs are taken, and taken at the correct times. <u>It may be that the dose of immunosuppression needs to be reduced or even stopped in certain situations, but this should never be done without discussion with the nephrology team</u>. Some of the immunosuppressive drugs have significant interactions with other drugs; the BNF or ICU pharmacist should be consulted. Details are also available from the Renal Unit Junior Doctors Handbook, available via the intranet.

- Steroids. These should always be continued especially on the ICU in times of stress. If there is any concern about GI absorption then it should be change to IV hydrocortisone. 5mg of prednisolone is equivalent to 20mg of hydrocortisone.

- Ciclosporin (Neoral). The dose of ciclosporin is adjusted according to blood levels. The timing of the level is usually two hours after having taken the drug (C2 level) and ideally needs to be compared with the patient's previous levels. High levels can acutely lead to toxicity which can be seen as hyperkalaemia, hypertension, tremor and worsening graft function. Over a prolonged period of time ciclosporin can cause chronic damage to the kidney. If ciclosporin cannot be given orally then it should be given intravenously, the important point is that the intravenous dose is 1/3 of the oral dose. The dosing frequency should still be adhered to (i.e. bd). It should also be remembered that there are some significant drug interactions with ciclosporin (e.g. erythromycin). The BNF or ICU pharmacist should always be consulted when prescribing other drugs. Note, oral ciclosporin is prescribed as Neoral, a particular formulation of the drug.

- Tacrolimus. Tacrolimus is similar to ciclosporin in that it is adjusted according to drug levels. It is also nephrotoxic acutely and over a prolonged period of time. Tacrolimus can also cause a cardiomyopathy and promote diabetes. When being given intravenously, the intravenous dose is 1/5 the oral dose given as a continuous infusion. The levels take a while to come back, check with the transplant team when the want levels, they should not just be done as routine.

- Azathioprine. AZA can suppress the bone marrow and therefore needs to be monitored closely especially when first starting. It has a dangerous interaction with allopurinol. The intravenous and oral doses are the same.

- Mycophenolate mofetil. This is similar to AZA but can cause GI upset. The intravenous doses and oral doses are the same.

Complications of renal transplants

Most of the complications relate to the drugs used. As a high level of immunosuppressive treatment is given near the beginning, the first 12 months are a high risk period for infections, including opportunistic infections such as pneumocystis and cytomegalovirus.

Patients may need to be admitted immediately post op due to technical complications (e.g. bleeding) but it is more usual for them to present either with sepsis or non (immediately related) transplant issues (e.g. coronary artery disease, post surgery).

Specific management of RTx patients on the ICU

1. Remember their drugs (see above), do not change doses unless direct to
2. Avoid (where possible) femoral lines on same side as transplant
3. If they have a functioning fistula – do all you can to ensure it stays functioning (see above)
4. The management of AKI is still the same (pressure, volume, flow) but make sure an early graft ultrasound scan is done to exclude obstruction and ensure that the kidney is still perfused. If the transplant team feel that this AKI may be acute rejection they will consider a graft biopsy

Further reading

Note: This is not an exhaustive list – just a few pointers of some interesting articles (and there are lots more out there as well!)

Clinical guidelines and recommendations

NCEPOD report (2009). Acute kidney injury: adding insult to injury
http://www.ncepod.org.uk/2009aki.htm

KDIGO (Kidney Disease: Improving Global Outcomes) guidelines for AKI:
http://kdigo.org/home/guidelines/acute-kidney-injury/
For a summary: Diagnosis, evaluation and management of acute kidney injury: a KDIGO summary (Part 1). Kellum JA, Lameire N. Crit Care 2013; 17: 204

NICE Clinical Guideline 169 (2013) Acute Kidney Injury: Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy
http://publications.nice.org.uk/acute-kidney-injury-cg169

Acute kidney injury

1. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) group. Bellomo R, Ronco C, Kellum JA et al. Crit Care 2004; 8: R204-R212 [The origins of RIFLE]
2. The diagnosis of acute renal failure in intensive care: mongrel or pedigree? Tillyard A, Keays R, Soni N. Anaesthesia 2005; 60: 903-914 [A good review]
3. Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. Bellomo R, Kellum JA, Ronco C. Intensive Care Med 2007; 33: 409-413
4. Epidemiology of acute kidney injury: How big is the problem? Hoste EAJ, Schurgers M. Crit Care Med 2008; 36(4): S146-S151
5. Prerenal failure: from old concepts to new paradigms. Macedo E, Mehta RL. Curr Opin Crit Care 2009; 15: 467-473 [A good review of the pathophysiology behind pre renal failure]
6. Prevention of acute kidney injury and protection of renal function in the intensive care unit. expert opinion of the working group for nephrology, ESICM. Joannidis M, Druml W, Forni LG, Groeneveld AB, Honore P, Oudemans-van Straaten HM, et al. Intensive Care Med. 2010;36:392–411
7. Acute kidney injury in the Intensive Care Unit: An update and primer for the intensivist. Dennen P, Douglas IS, Anderson R. Crit Care Med 2010; 38(1); 261-275
8. Health services Journal June 2011 Suppl 1 [A series of interesting articles looking at the economic impact of AKI and efforts to reduce its incidence] http://www.hsj.co.uk/Journals/2/Files/2011/6/23/HSJ_Supplement_acutekidneyinjur_23june.pdf
9. Biomarkers for the prediction of acute kidney injury: a narrative review on current status and future challenges. De Geus HRH, Betjes MG, Bakker J. Clin Kidney J. 2012; 5: 102-108
10. Novel biomarkers of acute kidney injury and failure: clinical applicability. Martensson J, Martling CR, Bell M. Br J Anaesth. 2012; 109 (6): 843-50
11. Acute kidney injury in the critically ill: Is iodinated contrast medium really harmful? Ehrmann S, Baldin J, Savath L et al. Crit Care Med 2013; 41:1017–1026
12. Kidney attack: overdiagnosis of acute kidney injury or comprehensive definition of acute kidney syndromes? Ronco C. Blood Purif 2013; 36: 65-68

Continuous renal replacement therapy

1. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Ronco C, Bellomo R, Homel P et al. Lancet 2000; 355: 26–30
2. Continuous versus intermittent renal replacement therapy: A meta-analysis. Kellum JA, Angus DC, Johnson JP, Leblanc M, Griffin M, Ramakrishnan N, et al. Int Care Med. 2002;28:29–37
3. Continuous is not continuous: the incidence and impact of circuit "down-time" on uraemic control during continuous veno-venous haemofiltration. Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R. Intensive Care Med. 2003;29:575–578.
4. Anticoagulation strategies in continuous renal replacement therapy: can the choice be evidence based? Oudemans-van Straaten HM, Wester JPJ, de Pont ACJM et al. Intensive Care Med 2006; 32: 188-202
5. A practical citrate anticoagulation continuous venovenous hemodiafiltration protocol for metabolic control and high solute clearance. Tolwani AJ, Prendergast MB, Speer RR, Stofan BS, Wille KM. Clin J Am Soc Nephrol. 2006;1:79–87
6. Continuous renal replacement therapy: a worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. Kidney) investigators. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, et al. Int Care Med. 2007;33:1563–1570
7. Drug dosing in continuous renal replacement therapy: general rules. Schetz M. Curr Opin Crit Care 2007; 13: 645-651
8. Intensity of renal support in critically ill patients with acute kidney injury. The VA/NIH Acute Renal Failure Trial Network. N Engl J Med 2008;359
9. Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury. Vesconi S, Cruz D, Fumagalli R, Kindgen-Milles D, Moni G, Marinho A, et al. Crit Care. 2009;13:57
10. Dosing of renal replacement therapy in acute kidney injury: Lessons learned from clinical trials. Bouchard J, Macedo E, Mehta RL. 2010; 55: 570-579
11. Management of the dialysis patient in general intensive care. Arulkumaran N, Montero RM, Singer M. Br J Anaesthesia 2012; 108(2): 183-92

Books

1. Atlas of haemofiltration. Bellomo R, Baldwin I, Ronco C, Golper T. Saunders. 2002 (ISBN-10: 0702025046)
2. Renal failure and replacement therapies. Blakeley S. Springer. 2008 (ISBN-10: 184628936X)
3. Critical Care Nephrology. Ronco C, Bellomo R, Kellum J. Saunders. 2009 (ISBN-10: 1416042520)