The critically ill kidney

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ABSTRACT
Acute kidney injury is a common finding in the critically ill patient. It carries a mortality of up to 60.3%. This review covers the definition, early detection and management of acute kidney injury. The review explores current controversies in the prescribing of renal replacement therapy and focuses on the prevention and management of contrast induced nephropathy.

Defining renal dysfunction

The syndrome of acute renal failure (ARF) is frequently encountered in hospitalised patients with an estimated prevalence ranging from 1.5% to 24%. A recent large multicentre, multinational study cites the prevalence of ARF in the critically ill as 5.7%,[1] of which two-thirds of these patients will need renal replacement therapy (RRT). Disturbingly, the overall hospital mortality rate of all ICU patients with ARF was 60.3%.[1] Much debate has raged over the definition of ARF. Renal injury is not a discrete entity but is a continuum from subclinical dysfunction to complete renal failure. The term Acute Kidney Injury (AKI) has been adopted by the Critical Care community to reflect this broad clinical spectrum.[2]

Wide variations in the definition of AKI make it hard to compare results between studies and populations, making the interpretation of data from clinical trials very difficult. In 2002, the Acute Dialysis Quality Initiative (ADQI) reported that over thirty five definitions of ARF were used in the literature[3] leading to the proposal of the RIFLE classification in 2004 (Table I).[4] RIFLE is the first classification to use the standardised nomenclature to describe AKI. It describes acute kidney injury as an abrupt (within 48 hours) reduction in kidney function and separates renal dysfunction into categories in terms of the degree of renal insult:

R isk of renal dysfunction
I njury to the kidney
F ailure of kidney function
L oss of kidney function
E nd-stage renal disease

The degree of renal dysfunction, according to the RIFLE criteria, is determined by the worst value of *either* urine output or an assessment of the glomerular filtration rate (GFR). It is much easier to measure the urine output or the serum creatinine as a surrogate of the GFR. The RIFLE criteria have been extensively validated,[5-7] with studies showing that they have clinical relevance for the diagnosis, monitoring of progression, and classification of the severity of AKI. The RIFLE criteria also have the ability to predict mortality in both hospitalised patients and the critically ill.

Subsequently, the RIFLE criteria were modified by the Acute Kidney Injury Network (AKIN) in 2007[8] (Table II) when categories for 'Loss' and 'End-stage kidney disease' were removed from the staging system. Individuals who receive RRT are considered to have met the criteria for AKIN stage 3 irrespective of the stage they are in at the time of RRT. The AKIN classification stipulates that the changes in creatinine occur within a 48-hour period and that urinary tract obstruction, or other easily reversible causes of reduced urinary output, be excluded.

Detecting renal dysfunction

The clinical assessment of renal dysfunction relies on the detection of changes in surrogate markers of GFR, most frequently through the measurement of serum urea and creatinine. This may lead to inaccuracies of the assessment of renal disease since both creatinine and urea are influenced by many other factors. They do not reflect dynamic changes, and only exceed normal values when there is already substantial loss of renal function. The recent literature centres on the quest to find early markers for

Table I: RIFLE criteria

	GFR criteria	Urine output criteria	Hospital mortality rate[6]
Risk	↑Serum creatinine x 1.5 or ↓GFR > 25%	< 0.5 ml/kg/hr x 6 hours	20.9%
Injury	↑Serum creatinine x2 or ↓GFR > 50%	< 0.5 ml/kg/hr x 12 hours	45.6%
Failure	↑Serum creatinine x3 or ↓GFR > 75%	< 0.3 ml/kg/hr x 24 hours or Anuria x 12 hours	56.8%
Outcome categories			
Loss	Complete loss of renal function for > 4 weeks		
End stage renal disease	Need for RRT for ≥ 3 months		

Table II: Classification/staging system for acute kidney injury[8]

Stage	Serum creatinine	Urine output
1	↑ in sCr* ≥ 26.4 µmol/l, or ↑ to ≥ 1.3–2 x from baseline	< 0.5 ml/kg/hr for > 6 hours
2	↑ in sCr* to ≥ 2–3 x from baseline	< 0.5 ml/kg/hr for > 12 hours
3	↑ to >3x from baseline, or sCr* of ≥ 354µmol/l with an acute increase of > 44 µmol/l	<0.3 ml/kg/hr for > 24 hours, or Anuria x 12 hours

*sCr serum creatinine

acute kidney injury, since early detection may allow preventive and possible therapeutic measures, thus avoiding further insults and progression to overt renal failure.

Many biomarkers for AKI have been detected in the urine making them minimally invasive tests with the potential for patient self-testing. Unfortunately, urinary detection is uncertain with severe oliguria and interpretation may be inaccurate in the setting of diuretic therapy. An important advance has been the detection of plasma biomarkers for AKI.

Current biomarkers include:
- Neutrophil gelatinose associated lipocalin (NGAL) (urine and serum)
- Cystatin C (serum)
- Kidney injury molecule-1 (KIM-1) (urine)
- Interleukin 18 (urine)

The protein, neutrophil gelatinose associated lipocalin (NGAL), is a marker of tubular cell injury and is expressed in very low levels in the stomach, lungs, colon and kidney. Serum levels rise markedly after epithelial damage and the increase is seen within three hours following ischaemic or nephrotoxic injury. NGAL is the most sensitive and specific of the biomarkers currently under investigation.[9]

Cystatin C is a protein secreted by all nucleated cells and is minimally influenced by weight, sex, race, age and muscle mass. It mostly reflects a reduction in glomerular filtration rate rather than acting as a marker of renal injury. In the critically ill, a 50% increase in levels of serum cystatin C herald the occurrence of AKI one to two days before serum creatinine levels began to rise.[10]

KIM-1 is a protein that is over-expressed in cells of the proximal renal tubule after ischaemic or nephrotoxic insults. Urinary KIM-1 is used to distinguish ischaemic AKI (in which the levels are much higher) from pre-renal disease and chronic renal disease.[11]

Interleukin-18 is induced in the proximal renal tubule after AKI and appears to be useful in the differentiation of acute tubular necrosis from other types of renal disease, as it is not elevated in chronic kidney disease, urinary tract infection or pre-renal failure.

Renal replacement therapy

Renal replacement therapy (RRT) is a blood purification technique using the principles of diffusion and ultrafiltration. During RRT the concentration of the solute in the blood is altered by exposing the blood to another solution (dialysate) across a semipermeable membrane (filter).

Dialysis relies on the principle of diffusion, and is responsible for the removal of solute as a result of random molecular motion. The amount of solute removed depends upon the concentration gradient, the molecular weight, the speed of motion of the molecules, their molecular size, and the resistance of the membrane.

Haemo- and ultrafiltration require a driving pressure and remove mostly fluid. Solute is removed along with the fluid by the process of convective transport, known as solvent drag.

During dialysis (Figure 1a), the solutes diffuse across the membrane that separates the blood from the dialysate. The dialysate flows in the opposite direction to the blood to maximise solute removal. Small solutes, such as urea, diffuse readily and are easily removed whereas larger solutes (e.g. low molecular weight proteins) are cleared less effectively.

Figure 1a: Dialysis

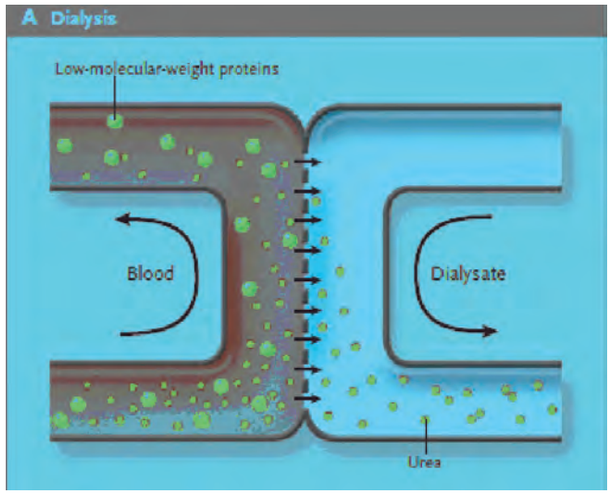
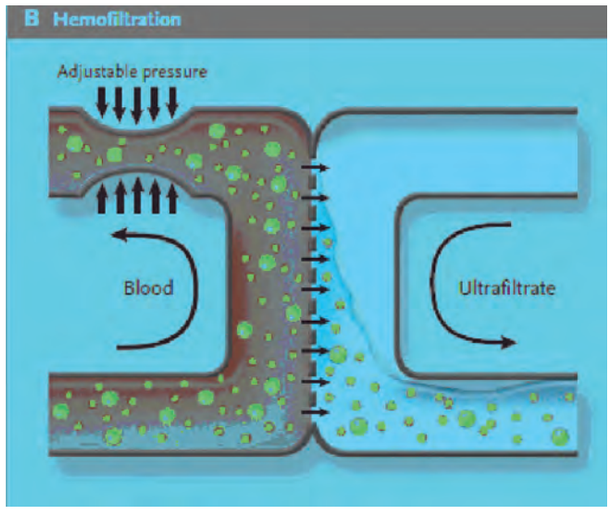


Figure 1b: Haemofiltration



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During haemofiltration (and ultrafiltration, Figure 1b) water is forced across the membrane due to the positive hydrostatic pressure applied to the blood compartment. Solutes are carried along with the fluid by convection. Compared to diffusion (as with dialysis), convection (haemofiltration) removes the larger

solutes at a similar rate to the smaller solutes. Haemodiafiltration is a combination of dialysis and high volume ultrafiltration.

The purpose of RRT is to mimic the functions and physiology of the kidney. Regardless of the mode of dialysis, the aim is to ensure adequate blood purification, whilst avoiding complications. RRT should be clinically well tolerated, whilst providing a homeostatic milieu that favours organ recovery.

Anticoagulation is required to prevent clotting in the external dialysis circuit. Heparin is most commonly used, but this exposes the patient to systemic anticoagulation and the risk of bleeding. Other methods of anticoagulation include the use of citrate, serine protease inhibitors (e.g. nafamostat mesylate), prostacyclin or heparinoids. A recent single-centre study found that anticoagulation of the external circuit with citrate was safer, better tolerated, and as effective as systemic anticoagulation with a low molecular weight heparin during continuous renal replacement.[14] The study also found that in patients receiving citrate anticoagulation there was a reduction in mortality and a faster return to renal recovery. At present, there is no consensus on anticoagulation and the choice of technique should be based on individual patient characteristics, ease of monitoring and local expertise.

Continuous haemodialysis

Continuous renal replacement techniques (CRRT) were developed in 1977. These are low-efficiency techniques relying mainly on convection.

The first described form of continuous renal replacement therapy was continuous arterio-venous haemofiltration (CAVH), shown in Figure 2. This requires both arterial and venous cannulation. Arterial blood, driven by patient's arterial pressure, flows through the filter where ultrafiltrate is skimmed off and the remaining blood returned to the patient via the venous cannula. Urea clearances were low and this technique was subsequently modified (Figure 3).

Figure 2: Continuous arterio-venous haemofiltration (CAVH)

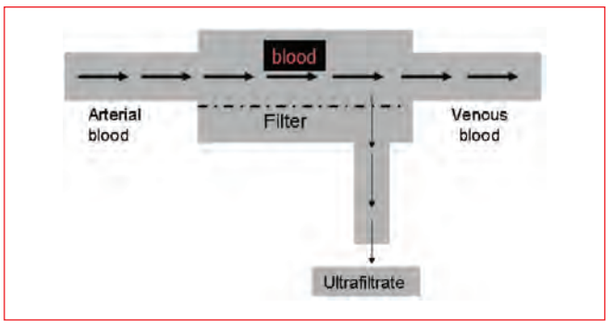
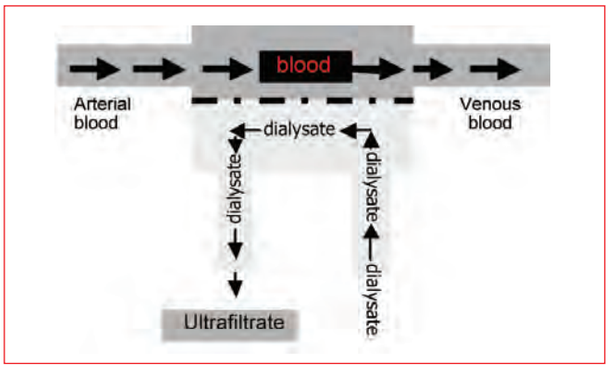


Figure 3: Continuous arterio-venous haemodiafiltration (CAVHD)



In continuous arterio-venous haemodiafiltration (CAVHD) a counter current dialysate was added in order to try to improve clearance (Figure 3). These techniques are seldom used today for a number of reasons, including the 15–20% morbidity due to arterial cannulation, and the requirement for a systolic blood pressure of at least 90 mm Hg to drive the blood flow (which is often not practical in the critically ill). The development of double lumen catheters and peristaltic blood pumps has led to improved methods.

Continuous venovenous haemofiltration – CVVH (Figure 4) and continuous venovenous haemodiafiltration – CVVHD (Figure 5) are both low-pressure systems. Since there is no arterial component to provide a driving pressure through the circuit, roller-pumps are necessary to create flow.

Figure 4: Continuous venovenous haemofiltration (CVVH)

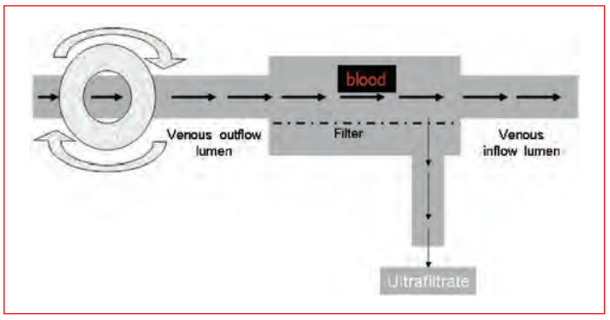
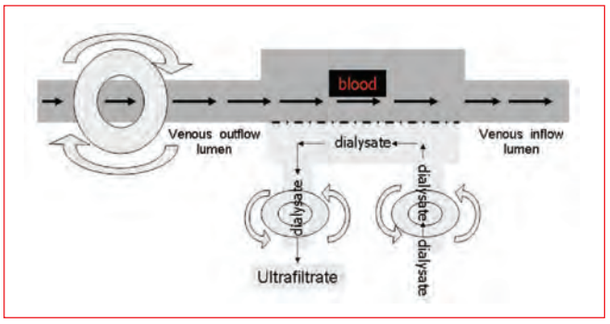


Figure 5: Continuous venovenous haemodiafiltration (CVVHD)



Both CVVH and CVVHD use a double lumen catheter inserted into a large vein. CVVHD is similar to CVVH but employs dialysate in a countercurrent mechanism to increase the clearance of waste products.

Intermittent dialysis

The principles employed in intermittent haemodialysis (IHD) are similar to the continuous methods, but the duration of dialysis is shorter (3–4 hours, every 1–2 days) and the dialysate flows are much higher to improve efficiency of clearance. The shorter duration of IHD necessitates large volume removal over short time periods, which may be poorly tolerated in the critically ill. Haemodialysis-associated hypotension is estimated to occur in approximately 20–30% of treatments and repeated hypotensive episodes may delay renal recovery. Solute removal is episodic and although the technique is efficient, there may be inferior urea and acid-base control than with the continuous techniques.

Sustained low-efficiency daily dialysis

Slow, or sustained, low-efficiency daily dialysis (SLEDD) is a hybrid technique of intermittent extended haemofiltration that is applied for about eight hours a day. It was first described in the early 1990s and has increased in popularity over the past

five years. As a hybrid technique it has the desirable properties of both IHD and CRRT namely:
1) Low efficiency solute removal compared to IHD, thus minimising disequilibrium
2) Reduced rate of ultrafiltration compared to IHD minimising haemodynamic disturbances
3) Sustained treatment to maximise delivered dose of dialysis
4) Less heparin requirements than CRRT
5) Usually performed overnight, minimising the interruptions to dialysis caused by therapeutic and diagnostic procedures (e.g. theatre visits, radiological interventions)[15]

Which modality is best?
The literature has failed to reach a consensus regarding the superiority of either intermittent or continuous dialysis techniques. Some studies have suggested that CRRT is superior to intermittent renal replacement therapy (IRRT) in terms of mortality, renal recovery and metabolic control, but other studies have failed to show significant differences in mortality in the ICU.[16,17] Since neither technique offers a superior survival benefit over the other, the modality used must be selected on an individual basis. IRRT is preferable if there is an increased bleeding risk (minimal time required for systemic anticoagulation whilst receiving dialysis and less damage to platelets from the shorter duration of exposure to the extracorporeal circuit). CRRT is preferable in the haemodynamically unstable patient as there is minimal deviation of blood volume and mean arterial pressure compared to intermittent techniques. CRRT is also the preferred modality in patients with cerebral oedema (e.g. in the setting of hepatic failure) as it reduces osmotic cellular shifts and the surge in intracranial pressure seen with IHD. Hybrid techniques (e.g. SLEDD) combine the benefits of both intermittent and continuous methods and are currently emerging as acceptable methods of renal replacement.

Who to dialyse?
This varies hugely between different units but a reasonable guide to the indications for acute haemodialysis is suggested below (Table III).

How much to dialyse?
In long-term dialysis patients, the delivered dose of RRT has an important impact on long-term morbidity and mortality.[19] The dose of RRT may also play a role in the outcome in patients with AKI. A greater dose of dialysis improves correction of metabolic disturbances, but may also result in more frequent episodes of hypotension. Hypotension could delay renal recovery by exacerbating ischaemia-reperfusion damage, particularly in the renal tubules.[20] A study performed by Schiffl et al in 2002 in the critically ill population showed a 28% mortality with daily dialysis compared to a 46% mortality in alternate day dialysis.[21] Surprisingly, daily dialysis was associated with less hypotension and a shorter time to renal recovery than continuous techniques. Higher ultrafiltration rates (35 ml/kg/h instead of 25 ml/kg/h) have been associated with a higher survival rate.[22] These studies are subject to interpretation however, as they were all single-centre studies.

In July 2008, a multicentre, randomised prospective controlled trial revealed no difference in mortality or improvement in recovery of renal function between intensive (dialysis six days a week) or less-intensive therapy (dialysis three days a week).[23] Hypotension, hypophosphataemia and hypokalaemia were observed more frequently in the intensive-therapy group. The inter-trial variations may, in part, be explained by the differences in delivered dialysis dose. In the Schiffl study,[21] the alternate day dialysis group received a dose of dialysis that was probably inadequate; whereas in the multicentre study, both groups received similar and adequate doses of dialysis. The implication of the studies is that it may not matter if the patients receive daily or alternate day dialysis, as long as the total dose of dialysis is adequate.[24]

When to dialyse?
Uraemia exerts profound effects on different biological functions, so it seems reasonable that earlier initiation of RRT and the avoidance of severe derangements in metabolic control should reduce the adverse effects of AKI. There are few well-constructed randomised controlled trials to support this hypothesis: certainly no benefit has been demonstrated if "prophylactic" haemofiltration is used in high risk groups in the absence of renal failure. A retrospective study showed improved survival with earlier initiation of RRT in posttraumatic AKI.[25] No clear guidance on the timing of RRT can be made at this time although expert opinion would recommend early intervention.[26]

Non-renal indications for RRT
Inflammatory mediators of septic shock (so called "middle molecules") have a molecular weight that is compatible with passage through the membranes used in CRRT. It has been postulated that removal of these inflammatory cytokines with haemofiltration may be an adjuvant treatment of sepsis. Experimental evidence suggests that sepsis mediators can be removed with RRT but this has yet to translate into outcome benefit.[27] Conversely, a recent study suggests that the early use of CRRT in the setting of severe sepsis may be harmful.[28] In a cohort of 76 patients, CRRT failed to limit or improve organ failure, failed to modify plasma cytokine levels and even prolonged the requirement for organ support. In addition, patients with severe sepsis receiving CRRT had a trend to higher mortality at 14 days compared with a control group, leading to premature discontinuation of the study.

Use of diuretics in acute kidney injury
Oliguria is a bad prognostic sign in patients with acute kidney injury. Evidence suggests that non-oliguric renal failure has a better prognosis than oliguric renal failure.[29] Attempts to convert oliguric into non-oliguric renal failure have not been conclusively found to improve outcome. Although it may be very gratifying to see urine in the catheter bag, the use of loop diuretics in the

Table III: Indications for acute haemodialysis

Uraemia	Fluid overload	Electrolytes/acid base	Intoxications with dialysable toxin	Non-renal causes
Azotaemia	Volume removal	K^+ > 6.5 mmol/l or rapidly rising	Ethanol, methanol	For drug/nutrition administration
Neuropathy, myopathy	Pulmonary oedema	Na+ < 110/>160 mmol/l	Barbiturates	Hyperthermia > 40°C
Encephalopathy	Oliguria < 200 ml/12h	Metabolic acidosis pH < 7.0	Theophylline	? eliminate inflammatory septic mediators
Pericarditis	Anuria < 50 ml/12 h		Salicylates	

critically ill patient with AKI does not prevent the progression from early kidney failure to more advanced stages of AKI and may even be harmful. From a pathophysiological point of view there are reasons why loop diuretics may have a beneficial effect in AKI (improved renal blood flow, reduction in renal oxygen consumption, prevention of tubular obstruction). This has not been borne out conclusively in clinical trials. Loop diuretics do not stave off incipient renal failure, nor do they reduce the need for renal replacement therapy or promote renal recovery.[30-32] Boluses of furosemide may cause hypotension thus compounding the injury to the kidney and, in addition, may cause distant organ damage i.e. ototoxicity.[31] A recent study by Mehta et al found that the clinical use of diuretics in patients with AKI was associated with non-recovery of renal function and an increased risk of death.[33] However, this trial has been criticised due to the use of propensity score models which may skew data.[34] At present there is discord in the literature suggesting there is clinical equipoise with regards to the use of loop diuretics and outcome in AKI.[30]

Contrast induced nephropathy

Contrast induced nephropathy (CIN) is frequently seen in the critically ill patient and is the third most common cause of hospital-acquired acute renal failure in the USA. It is defined as:

- An absolute increase in serum creatinine of > 44 mol/l or
- A relative increase in serum creatinine of 25% from baseline
- With no alternative aetiology
- Within three days after the administration of contrast media[35,36]

The incidence of CIN depends on the presence of pre-existing renal dysfunction: occurring in 3.3–8% in patients with no pre-existing renal impairment, and in 12–26% if there is concurrent renal disease.[37-39] Other risk factors include diabetes, advanced age, congestive cardiac failure, hypovolaemia, concomitant use of nephrotoxic drugs and the volume and type of contrast media administered.

The pathogenesis of CIN is incompletely understood. Iodinated, high osmolar, ionised contrast media appear to be the culprits. Contrast media may cause prolonged intra-renal vasoconstriction and medullary hypoxia or may have a direct cytotoxic action on the tubular epithelial cells.[40] Debate rages in the literature as to whether or not iso-osmolar contrast media are less nephrotoxic than hypo-osmolar agents. It is likely that the osmolality of the contrast media is not the only determinant of CIN and that viscosity also plays a role.

Less than 5% of patients with CIN go on to require RRT. However, the need for RRT carries a high mortality risk. The in-hospital mortality for a patient with CIN has been reported to be between 7.1% and 22%;[38-41] if RRT is required, the in-hospital mortality is 35.7% and by two years the mortality rate rises to 81.2%. It is difficult to assess the true impact of CIN on mortality, as many of the mortality data are from retrospective studies. It is not clear whether CIN is responsible for the high death rate or whether predisposed patients are sicker, have more comorbidity and thus are at greater risk of dying.[42] Even after adjusting for comorbid disease, a cohort study of patients with contrast-induced AKI had a 5.5-fold increased risk of death.[37]

There have been many attempts to find a preventative therapy for CIN, most studies having been performed in patients who are not critically ill. At present it is difficult to make firm recommendations about prevention and treatment of CIN in the critically ill.[43] In the general population, pre-hydration seems the most effective. The rationale for periprocedural hydration is to decrease the activity of the renin–angiotensin system, reduce vasoconstrictive hormones (e.g. endothelin), increase sodium diuresis, prevent tubular obstruction and dilute the contrast medium in the tubule, thereby decreasing nephrotoxic effects. It is recommended patients be given 1–2 ml/kg/h of normal saline for the 12 hours prior to contrast administration, and for 6 hours post-administration. Normal saline is superior to 0.45% saline.[44] Oral hydration can also be used but is not as effective as intravenous therapy.[45]

N-acetyl cysteine (NAC), a powerful antioxidant and vasodilator, potentially reduces CIN. NAC is an abundant source of sulfhydryl groups and acts as a free radical scavenger. Meta-analyses have shown conflicting results with regards to benefit in the prevention of CIN.[46,47] In the setting of clinical equipoise, whilst caution should be heeded with using NAC as a universal prophylactic agent, NAC does have a favourable profile and its toxic effects are minimal. It is probably best used in those patients at highest risk of CIN (i.e. those with chronic kidney disease and diabetes). It may be that the reduction in serum creatinine by NAC is an artificial effect. NAC may cause active secretion of creatinine by the renal tubules, thereby lowering the serum levels. If Cystatin C is used as a biomarker for CIN, there is no drop in the level of Cystatin C with NAC prophylaxis.[48] It may therefore be a false impression that NAC is protective against CIN.

Sodium bicarbonate potentially alkalinises renal tubular fluid, which in turn reduces the generation of oxygen free radicals.[45] Sodium bicarbonate has been found to be protective in small prospective trials, but a recent study of 353 patients in 2008 failed to show a difference in the prevention of CIN.[49] This trial has been criticised for using low doses of sodium bicarbonate in a hyperosmolar mixture. A 2009 meta-analysis of 17 randomised controls concluded that the administration of sodium-bicarbonate-based fluids significantly reduces the risk of CIN compared to NAC, and to other standard prophylactic hydration regimens, but does not reduce the need for RRT, nor does it decrease the mortality due to CIN. The meta-analysis found that sodium bicarbonate rehydration reduces the risk of CIN by 54–83% to an overall incidence of CIN 8%.[50]

Many strategies have been evaluated in the prevention of CIN prophylaxis. A recent meta-analysis by Kelly et al[51] shows that:

1. NAC is more protective than hydration alone
2. Theophylline may reduce the risk of development of CIN
3. Furosemide increases the risk for development of CIN

Strategies to prevent CIN have been divided into those showing possible benefit (prophylactic haemofiltration, theophylline, prostacyclin as well as sodium bicarbonate and NAC), and those of doubtful benefit (ascorbic acid, calcium channel blockers, haemodialysis, statins, dopamine and the selective dopamine-receptor-1 agonist: fenoldapam).[52] The use of diuretics and mannitol may be harmful.

Current recommendations in the prevention of CIN include the use of intravenous hydration combined with the use of a low volume of low or iso-osmolar contrast medium. In high risk patients non-iodinated agents should be used as the preferred contrast media. Concurrent nephrotoxics should be avoided and the use of metformin should be withheld for 48 hours prior to exposure to contrast until it has been established that CIN has not occurred.[52] The results of trials with erythropoietin and the antioxidant Mesna (sodium 2-mercaptoethane sulfonate) are awaited.

Performing an MRI scan instead of a contrasted CT scan does not necessarily avoid the problem of AKI. Gadolinium is a paramagnetic metal that is commonly used as a contrast agent during MRI scans. Although initially believed to be safe, it is now known to be associated with nephrogenic systemic fibrosis (a condition with similar features to systemic sclerosis).[53] Gadolinium is absolutely contraindicated in patients with chronic kidney disease.

Why the fuss?

Acute kidney injury is an independent risk factor for both morbidity and mortality. The in-hospital mortality of patients with AKI ranges from 30% in patients with drug-induced injury up to 90% in patients with sepsis and multi-organ failure. Sepsis is the commonest cause of AKI in the ICU. The APACHE II scoring system recognises the impact of acute renal dysfunction on morbidity, awarding twice the number of allocated points to patients who develop AKI. It is evident that patients die because of renal failure and RRT does not remove the mortality

risk. It is essential that steps are taken to offer early maximum protection to the kidneys in the intensive care unit. The use of biomarkers to detect early renal dysfunction may prove useful in this regard.

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Declarations

I declare that I have no financial or personal relationship(s) which may have inappropriately influenced me in writing this paper.

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References:

1 Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005;294(7):813–818.
2 Han WK, Bonventre JV. Biologic markers for the early detection of acute kidney injury. Curr Opin Crit Care 2004;10(6):476–482.
3 Kellum JA, Mehta RL, Angus DC, Palevsky P, Ronco C. The first international consensus conference on continuous renal replacement therapy. Kidney Int 2002;62(5):1855–1863.
4 Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. 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. Crit Care 2004;8(4):R204–R212.
5 Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 2006;10(3):R73.
6 Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med 2007;35(8):1837–1843.
7 Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 2006;34(7):1913–1917.
8 Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11(2):R31.
9 Parikh CR, Devarajan P. New biomarkers of acute kidney injury. Crit Care Med 2008;36(4 Suppl):S159–S165.
10 Herget-Rosenthal S, Marggraf G, Husing J, Goring F, Pietruck F, Janssen O, et al. Early detection of acute renal failure by serum cystatin C. Kidney Int 2004;66(3):1115–1122.
11 Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int 2002;62(1):237–244
12 Parikh CR, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin 18 is a marker of human acute tubular necrosis. Am J Kidney Dis 2004;43(3):405–414.
13 Meyer TW, Hostetter TH. Uremia. N Engl J Med 2007;357(13):1316–1325.
14 Oudemans-van Straaten HM, Bosman RJ, Koopmans M, van der Voort PH, Wester JP, van der Spoel JI, et al. Citrate anticoagulation for continuous venovenous hemofiltration. Crit Care Med 2009;37(2):545–552.
15 Marshall MR, Ma T, Galler D, Rankin AP, Williams AB. Sustained low-efficiency daily diafiltration (SLEDD-f) for critically ill patients requiring renal replacement therapy: towards an adequate therapy. Nephrol Dial Transplant 2004;19(4):877–884.
16 Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. Crit Care Med 2008;36(2):610–617.
17 Uchino S. Choice of therapy and renal recovery. Crit Care Med 2008; 36(4 Suppl):S238–S242.
18 Davenport A, Finn R, Goldsmith HJ. Management of patients with renal failure complicated by cerebral oedema. Blood Purif 1989;7(4):203–209.
19 John S, Eckardt KU. Renal replacement strategies in the ICU. Chest 2007;132(4):1379–1388.
20 Manns M, Sigler MH, Teehan BP. Intradialytic renal haemodynamics--potential consequences for the management of the patient with acute renal failure. Nephrol Dial Transplant 1997;12(5):870–872.
21 Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. N Engl J Med 2002;346(5):305–310.
22 Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. Lancet 2000;356(9223):26–30.
23 Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, et al. Intensity of renal support in c ritically ill patients with acute kidney injury. N Engl J Med 2008;359(1):7–20.
24 Bonventre JV. Dialysis in acute kidney injury--more is not better. N Engl J Med 2008;359(1):82–84.
25 Gettings LG, Reynolds HN, Scalea T. Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs. late. Intensive Care Med 1999;25(8):805–813.
26 Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. J Crit Care 2009;24(1):129–140.
27 De Vriese AS, Vanholder RC, Pascual M, Lameire NH, Colardyn FA. Can inflammatory cytokines be removed efficiently by continuous renal replacement therapies?. Intensive Care Med 1999;25(9):903–910.
28 Payen D, Mateo J, Cavaillon JM, Fraisse F, Floriot C, Vicaut E. Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: a randomized controlled trial. Crit Care Med 2009;37(3):803–810.
29 Anderson RJ, Linas SL, Berns AS, Henrich WL, Miller TR, Gabow PA, et al. Nonoliguric acute renal failure. N Engl J Med 1977;296(20):1134–1138.
30 Bagshaw SM, Bellomo R, Kellum JA. Oliguria, volume overload, and loop diuretics. Crit Care Med 2008;36(4 Suppl):S172–S178.
31 Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. BMJ 2006;333(7565):420.
32 van der Voort PH, Boerma EC, Koopmans M, Zandberg M, de Ruiter J, Gerritsen RT, et al. Furosemide does not improve renal recovery after hemofiltration for acute renal failure in critically ill patients: a double blind randomized controlled trial. Crit Care Med 2009;37(2):533–538.
33 Mehta RL, Pascual MT, Soroko S, Chertow GM. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. JAMA 2002; 288(20):2547–2553.
34 Uchino S, Doig GS, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Diuretics and mortality in acute renal failure. Crit Care Med 2004;32(8):1669–1677.
35 Barrett BJ, Parfrey PS. Prevention of nephrotoxicity induced by radiocontrast agents. N Engl J Med 1994; 331(21):1449–1450.
36 Thomsen HS, Morcos SK. Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) guidelines. Br J Radiol 2003;76(908):513–518.
37 Levy EM, Viscoli CM, Horwitz RI. The effect of acute renal failure on mortality. A cohort analysis. JAMA 1996;275(19):1489–1494.
38 McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. Am J Med 1997;103(5):368–375.
39 Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002;39(5):930–936.
40 Brezis M, Rosen S. Hypoxia of the renal medulla--its implications for disease. N Engl J Med 1995;332(10):647–655.
41 Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002;105(19):2259–2264.
42 Rudnick M, Feldman H. Contrast-induced nephropathy: what are the true clinical consequences?1. Clin J Am Soc Nephrol 2008;3(1):263–272.
43 van den BG, Tonino S, de Fijter C, Smit W, Schultz MJ. Bench-to-bedside review: preventive measures for contrast-induced nephropathy in critically ill patients. Crit Care 2005;9(4):361–370.
44 Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 2002;162(3):329–336.
45 Weisbord SD, Palevsky PM. Prevention of contrast-induced nephropathy with volume expansion. Clin J Am Soc Nephrol 2008;3(1):273–280.
46 Nallamothu BK, Shojania KG, Saint S, Hofer TP, Humes HD, Moscucci M, et al. Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. Am J Med 2004;117(12):938–947.
47 Pannu N, Manns B, Lee H, Tonelli M. Systematic review of the impact of N-acetylcysteine on contrast nephropathy. Kidney Int 2004;65(4):1366–1374.
48 Hoffmann U, Fischereder M, Kruger B, Drobnik W, Kramer BK. The value of N-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. J Am Soc Nephrol 2004;15(2):407–410.
49 Brar SS, Shen AY, Jorgensen MB, Kotlewski A, Aharonian VJ, Desai N, et al. Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. JAMA 2008;300(9):1038–1046.
50 Kanbay M, Covic A, Coca SG, Turgut F, Akcay A, Parikh CR. Sodium bicarbonate for the prevention of contrast-induced nephropathy: a meta-analysis of 17 randomized trials. Int Urol Nephrol 2009.
51 Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med 2008;148(4):284–29
52 Sterling KA, Tehrani T, Rudnick MR. Clinical significance and preventive strategies for contrast-induced nephropathy. Curr Opin Nephrol Hypertens 2008;17(6):616–623.
53 Thomsen HS, Morcos SK, Dawson P. Is there a causal relation between the administration of gadolinium based contrast media and the development of nephrogenic systemic fibrosis (NSF)? Clin Radiol 2006;61(11):905–906.