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*Review*

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**Management of Sepsis-Induced Acute Kidney Injury**Senaka Rajapakse<sup>1</sup>, Chaturaka Rodrigo<sup>2</sup>, Eranga Wijewickrema<sup>2</sup><sup>1</sup>Department of Clinical Medicine, Faculty of Medicine, University of Colombo, Sri Lanka<sup>2</sup>University Medical Unit, National Hospital, Colombo, Sri Lanka**Abstract**

Acute kidney injury (AKI) occurs in a significant proportion of patients with severe sepsis, and is an important cause of mortality in such patients. Current concepts of pathogenesis of AKI are shifting from vasoconstriction-ischaemia induced injury to toxic and immune mediated injury and hyperaemic injury resulting in apoptosis of renal cells. Renal replacement therapy is the mainstay of management of AKI. Adequacy of dialysis is likely to be linked to better outcome, but there is still no clear consensus on the timing, modality, intensity or frequency of dialysis. Haemodynamically unstable patients usually require modes of continuous renal replacement therapy. Biocompatible dialyser membranes are likely to be safer than older cellulose membranes. Bicarbonate is preferred to acetate and lactate as dialysate buffer. Anticoagulation has to be undertaken with care to prevent excessive haemorrhage in the setting of already deranged haemostasis. Adequate volume resuscitation and maintenance of renal perfusion by the use of vasopressors is beneficial; norepinephrine is the vasopressor of choice. There is no place for the use of low- or renal-dose dopamine, mannitol or frusemide in the setting of sepsis-induced AKI, and in fact they may be detrimental. Prevention of kidney damage by nephrotoxic drugs and radio-contrast media is of vital importance. Careful dose management of nephrotoxic drugs will prevent renal injury. Hydration prior to administration of contrast media prevents nephrotoxicity, but the benefit of N-Acetylcysteine is unclear. Tight glycaemic control may have renoprotective effects, though its place in the management of severe sepsis is now controversial. No clear evidence of benefit is seen with other newer therapies.

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**Introduction**

Deterioration of renal function over a short period is termed acute kidney injury (AKI). AKI has replaced the term acute renal failure, and is defined according the RIFLE criteria<sup>1</sup>. Sepsis is the presence of SIRS with infection. When acute kidney injury occurs in the presence of sepsis, without other clear and established non-sepsis related causes of AKI, it is considered sepsis-induced. AKI affects approximately 35% of intensive care unit (ICU) patients<sup>1</sup>, and around 50% of these are due to sepsis<sup>2</sup>. While AKI has an overall mortality rate of 45%; the mortality rate of sepsis-induced AKI is much higher, at over 70%<sup>1,3</sup>. The severity of AKI positively correlates with morbidity and mortality of ICU patients. A linear relationship has been demonstrated between the stage of AKI stage and mortality<sup>3</sup>.

A clear understanding of pathophysiology, prevention and treatment of sepsis-induced AKI is essential for critical care physicians. We review the evidence base for aspects of renal replacement therapy, supportive therapies, and preventive aspects in sepsis-induced AKI.

**Pathophysiology of sepsis-induced AKI**

The pathophysiology of sepsis induced AKI is poorly understood. Traditionally, AKI in sepsis and septic shock is thought to result from renal ischaemia secondary to inadequate renal blood flow (RBF).

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This construct implies that restoration of RBF before acute tubular necrosis or cortical necrosis occurs should be the primary means of renal protection in septic patients with the risk of AKI. However, recent studies have shown that the renal circulation participates in the systemic vasodilatation observed during severe sepsis/septic shock, and the development of septic AKI occurs in the setting of adequate and even increased renal perfusion rather than renal hypoperfusion<sup>4,5</sup>. Thus, sepsis-induced AKI may represent a unique form of AKI, namely hyperaemic AKI. Microcirculatory changes which typically occur in other tissues in severe sepsis also occur in the kidney, resulting in tissue hypoperfusion despite normal macrovascular blood flow. It has been suggested that internal redistribution of blood flow occurs in sepsis, favouring the cortex and leading to medullary ischaemia and acute tubular damage. Nonetheless, in animal models, cortical and medullary blood flow measured by laser Doppler flowmetry remains unchanged in sepsis with hyperdynamic circulation<sup>6</sup>. The paucity of histological evidence from patients with sepsis-induced AKI is one reason for the poor understanding of its pathogenesis; most of our evidence is from surrogate markers of kidney damage, such as urine output, urinary sodium concentration, fractional excretion of sodium and fractional excretion of urea.

Toxic and immunologic mechanisms are clearly important in mediating renal injury during sepsis. This is due to the release of a vast array of inflammatory cytokines, arachidonate metabolites, vasoactive substances, thrombogenic agents, and other biologically active mediators. Tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) has been demonstrated to play a major role in pathogenesis of AKI in gram-negative septic shock<sup>7</sup>, through direct effects on glomerular endothelial and tubular cells resulting in apoptosis. Thus, the paradigms currently used to explain AKI in sepsis is shifting from vasoconstriction and ischaemia to vasodilatation and hyperaemia, and from acute tubular necrosis to acute tubular apoptosis.

## Modes of renal replacement therapy

### *Modalities of renal replacement therapy*

Renal replacement therapy is the mainstay of sepsis-induced AKI. While many modalities of renal replacement therapy are available, they all rely on two basic principles – diffusion and convection<sup>8</sup>. Dialysis depends primarily on diffusion, while haemofiltration uses convection. The two modalities may be combined.

### *Diffusion methods*

The two diffusion methods used are peritoneal dialysis and intermittent haemodialysis. Peritoneal dialysis, where the peritoneum acts as the semipermeable membrane, is rarely used in critically ill patients now. In this method, a peritoneal catheter is introduced through the anterior abdominal wall into the peritoneal cavity and a dialysis solution is cyclically introduced into and drained out from the peritoneal cavity. Urea, creatinine and other undesired molecules diffuse down their concentration gradients, and the solutes in the dialysate will readjust the constituents of plasma. If fluid removal is required, glucose is added to the dialysate to create ultrafiltration of water. An open randomised trial comparing peritoneal dialysis vs. haemofiltration in sepsis induced acute renal failure showed that peritoneal dialysis was both inferior as well as more expensive than haemofiltration<sup>9</sup>.

Intermittent haemodialysis is used in haemodynamically stable patients with ARF. Heparinized venous blood from the patient is made to pass through an extracorporeal dialyser, which separates it from a crystalloid solution by a semipermeable membrane. Urea, creatinine and other toxins pass down their chemical gradients into the dialysis solution while the reverse process restores the natural composition of plasma. By adjusting a pressure difference on either side of the membrane an osmotic drag can be created for water molecules to pass down into the dialysate, resulting in a net loss of water: this process, known as ultrafiltration, is used to remove fluid in fluid overloaded states. The major disadvantage of dialysis is that although it removes smaller molecules

such as urea efficiently, with 'middle' size (creatinine) and larger molecule the clearance can be quite unsatisfactory(8).

#### *Convective methods*

Haemofiltration is the commonly used convective modality. Blood is passed through a dialyser where it is separated from a crystalloid solution by a semipermeable membrane. A hydrostatic pressure is created on that side of the membrane to filter out most of the smaller and middle size molecules. This ultrafiltrate is discarded and replaced with a replacement fluid of desirable concentrations of solutes. Volume is managed by adjusting the volume of replacement fluid. Two methods of haemofiltration are used- continuous arteriovenous haemofiltration (CAVH) and continuous venovenous haemofiltration (CVVH). In CAVH the femoral artery is cannulated and blood is sent through an extracorporeal circuit. The arterial pressure drives the ultrafiltrate through the membrane. Though the design is simple, the method has the risk of a simple breach in the closed circuit resulting in exsanguination. Furthermore, the ultrafiltration rates achieved by arterial pressure alone are not adequate to clear solutes adequately as demanded, and clearance rates are even lower in hypotensive patients. Slow blood flow can result in frequent clotting of the extracorporeal circuit. In CVVH a vein (usually the femoral or internal jugular vein) is accessed. The venous blood is sent through an occlusive pump, which gives better control over filtration; and rates over 100 ml/min can be achieved. CVVH is currently the preferred modality of renal replacement therapy in critically ill patients, especially when they are haemodynamically unstable.

#### **The role of renal replacement therapy (RRT) in acute kidney injury**

The key issues in the use of renal replacement therapy are whether the modality, timing, and frequency of RRT influence mortality. These aspects are discussed in detail below.

#### *Modality of dialysis*

Continuous renal replacement therapy (CRRT) has an advantage over intermittent haemodialysis in that it provides greater haemodynamic stability, easier fluid removal and greater flexibility in providing parenteral nutrition as a result of greater control over fluid balance<sup>10,11</sup>. The disadvantages of continuous therapy are the need for long periods of anticoagulation of the patient to maximize the life span of the filter, complications related to vascular access, and greater economic cost.

Current evidence however, does not demonstrate a significant advantage of CRRT over IHD in terms of mortality or renal recovery. A recent meta-analysis by Bagshaw et al<sup>12</sup> comparing CRRT with IHD as the initial modality of renal replacement concluded that there was no significant difference in outcome in terms of mortality or renal recovery between the two modalities. It was suggested that CRRT resulted in fewer episodes of haemodynamic imbalance and better fluid balance; nonetheless the relevant studies had numerous flaws with regard to design, data description, conduct and quality. A systematic review Pannu et al<sup>13</sup> also showed that clinical outcomes with CRRT and IHD were similar. Overall, the current state of evidence does not indicate a clear advantage in the use of CRRT over IHD in sepsis induced ARF, although better quality evidence from large, multicentre trials are required. Given its advantages in patients who are haemodynamically unstable, CRRT is likely to be the more favoured modality where available. In haemodynamically stable patients, there is inadequate justification as yet to favour one modality over the other. In resource limited settings, IHD will remain the main modality of dialysis. Despite peritoneal dialysis being inferior, it may be the only available option in haemodynamically unstable patients in certain resource poor settings.

Whether dialysis or haemofiltration will help in removal of inflammatory mediators and hence help alleviate the cytokine storm in severe sepsis is unknown. Conventional ultrafiltration rates are probably inadequate to have a significant effect on cytokine removal, and for this

purpose High Volume Haemofiltration (HVHF), using ultrafiltration rates  $>35\text{ml/kg/hr}$  have been used. There is some evidence of improved haemodynamics, reduced need for vasopressor support<sup>14-16</sup> and a trend towards improved survival with HVHF<sup>17</sup>, but further studies are required. It has been suggested that the improved haemodynamics seen with CRRT may be a result of cytokine removal, and also mild hypothermia resulting in an increase systemic vascular tone.

#### *Timing of RRT*

The specific indications for initiation of RRT in sepsis induced ARF are different from those of chronic renal failure. The traditional indications seen in chronic renal failure such as encephalopathy and pericarditis are less common in AKI; also, these clinical features may be due to numerous other reasons in critical illness. Incipient or established fluid overload, electrolyte imbalance and acidosis which do not respond adequately to medical management are clear indications for initiation of RRT. Evidence regarding the ideal timing of dialysis is scarce. Three RCTs<sup>18-20</sup> have shown inconclusive results. A prospective cohort study<sup>21</sup> showed that the risk of death was lower when dialysis was started at lower blood urea levels. A specific blood urea nitrogen or creatinine level at which RRT should be commenced in ARF is difficult to define, and no firm recommendation can be made based on current evidence as to the ideal timing of initiation of RRT. Direct clinical or biochemical indications for RRT will guide the initiation of RRT in sepsis induced ARF. However, given the limited evidence of possible benefit in early initiation of RRT, it would seem logical to initiate RRT early rather than late, especially in rapidly developing, symptomatic, oliguric renal failure with metabolic derangement.

#### *Frequency and intensity of RRT*

The use of urea clearance alone as a measure of adequacy of dialysis has been questioned at recent times, as many other small and middle sized molecules contribute to the adverse effects of AKI.

This argument is further strengthened by the fact that in addition to urea and creatinine there may be many other 'small' and middle' size molecules that may contribute to the symptomatology of chronic renal failure. A Kt/V value of greater than 1 has been traditionally accepted as a measure of adequate dialysis in chronic renal failure. However, the high catabolic rate in sepsis induced ARF, variable fluid volumes, and the post-dialysis 'rebound' of urea concentrations from hypoperfused organs, limits the use of Kt/V as a measure of adequacy of dialysis in critically ill patients. The 'dose' of renal replacement therapy in IHD in acute renal failure is often described using the hours of dialysis, rate of blood flow, and frequency of dialysis. Since urea equilibrates rapidly across the dialysis membrane, urea clearance in CRRT is essentially equivalent to the volume of effluent dialysate (including any ultrafiltered fluid), and therefore CRRT dose is commonly expressed as L/kg per hour of effluent.

Gillum et al<sup>22</sup> prospectively studied the effect of dialysis intensity on survival in patients with ARF. The trial compared patients receiving intensive intermittent dialysis (daily dialysis with 5 -6 hours per treatment) and the other group had standard non-intensive prescription of 5 hour treatments from a daily basis to every third day basis. The survival in two groups did not vary significantly. The technical capacity of modern dialysers have increased significantly since then, and these findings have been challenged. Schiffl et al<sup>23</sup> in another trial demonstrated a higher survival among patients with ARF treated with daily IHD compared with those treated with thrice weekly IHD; the dose of dialysis in the conventional group was, however, lower than that recommended in chronic renal failure. In this study, patients needing CRRT were excluded, possibly resulting in exclusion of severely ill patients; hence the patient population may not be truly representative of the range of patients with sepsis induced AKI, many of whom would be in septic shock, needing CRRT. To further support this, the overall mortality of the study was 37%, which is much lower

than standard mortality rates for sepsis induced AKI.

Ronco et al<sup>24</sup> evaluated the dose effect on outcome of patients treated with CVVH. They randomized patients to three groups and prescribed three ultra filtration rates based on body weights for each group. (20, 35, 45 ml / hr / kg). A significant survival benefit was seen in patients who received middle and high ultrafiltration rates vs. the low filtration rate group. Thus it appears that a minimum ultrafiltration rate of 35 ml / kg / h is required to have a survival benefit. Significantly, this study highlighted the inadequacy of routine CVVH prescriptions and ultrafiltration rates used in most centers. Based on these findings, for successful haemofiltration the filtration fraction (ultrafiltration rate / blood flow rate) has to be around 30 - 35%, and to achieve an ultrafiltration rate of 35 ml/kg/h, a blood flow of at least 250 ml/min is necessary as opposed to the current rate around 150 ml/min used in most centres.

Contradicting this, results from the recent ATN trial do not support these findings, concluding that intensive RRT does not improve mortality or hasten recovery compared with non-intensive dialysis<sup>25</sup>. Overall, evidence regarding the ideal dose of renal replacement therapy in sepsis induced ARF is inadequate to make firm recommendations, and larger well-designed RCTs are required.

Other aspects related to RRT which must be considered are the type of semipermeable membrane used in the dialyser, and the type of buffer used, and issues related to anticoagulation. The semipermeable membrane that separates the body fluids and the crystalloid solution in the dialyser influences the efficiency of the procedure. Membranes are of two types- biocompatible membranes and others. Non-biocompatible membranes are thought to cause activation of inflammatory cells and thus the release of inflammatory mediators, resulting in bronchoconstriction, vasoconstriction and hypotension, which are clearly undesirable in the setting of sepsis.

Definite evidence that the possible pro-inflammatory effects has deleterious

effects in septic patients is not available. Early cellulose based versions of dialysis membranes were bio-incompatible, but modification of the cellulose component has made it possible to create synthetic polymers that are biocompatible. Biocompatible membranes may have the added advantage of adsorbing mediators involved in the sepsis cascade. Evidence from several RCTs<sup>26-29</sup> suggests that the use of non-biocompatible membranes is associated with an increased risk of death; hence their use is not recommended in acute renal failure. On the downside, synthetic membranes are more expensive.

Dialysate contains a buffer to correct metabolic acidosis - acetate, lactate and bicarbonate are used. In septic patients, the inadequacy of organs to convert lactate or acetate to bicarbonate is a potential issue -hence bicarbonate buffer is preferred on theoretical grounds. A comparison of bicarbonate and lactate in patients receiving CRRT showed no difference in survival, although cardiovascular events were significantly less with bicarbonate<sup>30</sup>. Overall, however, there is no evidence that bicarbonate is superior to acetate or lactate<sup>31</sup>, or that there is any difference between acetate and lactate<sup>32</sup>, although evidence is only from small studies.

Anticoagulation is required in both IHD and CRRT to prevent clotting of the filter in the extracorporeal circuit, and this is of particular importance in CRRT. Because of the coagulopathy which frequently occurs in severe sepsis, anticoagulation can result in serious bleeding.

Unfractionated heparin is most commonly used, although the optimal intensity of anticoagulation is not known. Fractionated heparin is not used because of the difficulties in reversing its effects. In patients at high risk of bleeding saline flushes or citrate infusion are used. There is some evidence that citrate reduces the risk of bleeding compared to heparin<sup>33</sup>, although it could cause hypocalcaemia, metabolic alkalosis and citrate toxicity. Hirudin maybe an alternative to heparin, but data is inadequate at present.

### Non-dialytic strategies for preventing and treating sepsis induced acute kidney injury

While clearly dialysis improves outcome in sepsis induced AKI, many other strategies are also of value. In particular, careful attention to hydration and volume loading, maintenance of mean arterial pressure using vasopressors and inotropes, and avoidance of ionic contrast agents and nephro-toxic drugs are of benefit.

#### *Hydration and volume loading*

Although no randomized controlled trials (RCTs) have been carried out, it has long been recognized that intravascular volume depletion is an important risk factor for development of AKI and its correction with fluids lead to resolution of AKI. Rivers et al<sup>34</sup> demonstrated that early aggressive resuscitation reduced mortality in septic shock, although direct evidence of prevention of AKI was not documented in the trial. In certain settings, such as rhabdomyolysis, early and aggressive fluid resuscitation has clearly been shown to be beneficial<sup>35</sup>.

#### *Maintaining renal perfusion pressure*

While clearly maintaining adequate renal perfusion is of paramount importance, recommendations are based more on expert opinion than trial evidence. In general, a mean arterial pressure above 65mmHg is considered adequate; however this value is arbitrary, and targets should be based on the physiological state of the patient, and other outcome measures such as urine output, measures of intravascular volume adequacy, and biochemical values.

The profound vasodilation which occurs in severe sepsis results in resistant shock and reduction in renal perfusion. Vasopressor agents-such as , high-dose dopamine, epinephrine, phenylephrine, or low dose vasopressin or terlipressin- can be used to restore an acceptable mean arterial blood pressure, once adequate volume repletion is accomplished. Despite previous fears that vasopressors may result in further renal vasoconstriction and reduced renal perfusion, evidence has been to the contrary- renal perfusion improves

significantly with norepinephrine in patients with septic shock<sup>36</sup>. This probably occurs partly due to the rise in mean arterial pressure and partly due to the renal vasodilatation caused by decreased renal sympathetic tone through baroreceptor stimulation by increase in systemic blood pressure<sup>37</sup>. Norepinephrine is superior to high-dose dopamine in restoring target blood pressure in septic shock, and is associated with lower mortality compared to other vasopressor agents<sup>38</sup>. Norepinephrine is currently the vasopressor of choice in septic shock. Phenylephrine and adrenaline are not recommended as first line agents because of concern regarding unbalanced vasoconstriction with phenylephrine, together with lack of sufficient human data, and in the case of adrenaline, concern about its greater tendency to induce hyperlactaemia, acidosis, hyperglycaemia and tachycardia. On the other hand, low-dose vasopressin, when used in combination with norepinephrine, allowed decreasing the dose of norepinephrine in the treatment of septic shock without demonstrating any other added benefit<sup>39</sup>.

Increased intra-abdominal pressure results in reduced renal perfusion. Prompt recognition and early surgical treatment of increased intra-abdominal pressure is often neglected, but of utmost importance<sup>40</sup>.

#### *Low-dose dopamine*

In healthy subjects, low-dose dopamine (0.5 to 3µg/kg/min) increases renal blood flow and promotes natriuresis through stimulation of renal D1, D2 and D4 receptors<sup>41</sup>. Based on this, so called low-dose dopamine or renal-dose dopamine has long been touted as being renoprotective.<sup>42,43</sup> However, repeated studies failed to demonstrate this benefit, and a recent meta-analysis showed no significant benefit in the use of low-dose dopamine, in reducing death or need for renal replacement therapy<sup>44</sup>. Low-dose or renal-dose has no place in the management of critically ill patients. This recommendation does not preclude the use of dopamine in higher, 'inotropic' doses.

*Drug induced nephrotoxicity*

Many patients with sepsis are critically ill often necessitating the use of multiple therapeutic agents, many of which may individually or in combination have the potential to cause kidney injury. Nephrotoxic drugs maybe a contributing factor in 19% to 25% of cases of severe acute renal failure in critically ill patients<sup>3,45</sup>. Nephrotoxicity occurs through various mechanisms.

Aminoglycosides, vancomycin and amphotericin B are the most commonly used drugs in septic patients which cause acute tubular necrosis (ATN). Toxicity results from sustained elevations of drug levels, that occur from multiple daily doses. Aminoglycosides show peak dependent bactericidal effects, and hence once daily dosing has been shown to minimise this effect without any effect on efficacy<sup>46-48</sup>. Vancomycin results in nephrotoxicity in 6% to 30% of patients<sup>49</sup>. Both peak and trough levels contribute to toxicity, and careful consideration of renal function, and monitoring of trough levels are essential with its use. Amphotericin B associated nephrotoxicity occurs in 25-30% of patients, with progressive increase in the risk of AKI with increase in cumulative dose<sup>50</sup>. The risk of renal dysfunction is relatively low at doses of  $<0.5\text{mg.kg}^{-1}\text{.day}$  and a cumulative dose of  $<600\text{mg}$ . The use of lipid formulations of amphotericin B seems to cause less nephrotoxicity compared with standard formulations<sup>51,52</sup>.

*Drug induced acute interstitial nephritis*

Many drugs, which are commonly used in the critical care setting, are associated with acute interstitial nephritis (NSAIDs, beta-lactams, sulphonamides, loop diuretics, thiazides, quinolones, cimetidine, allopurinol, proton pump inhibitors), and account for 3% to 15% of all drug induced acute renal failure<sup>53</sup>. Renal dysfunction usually occur 7-14 days after exposure and when it occurs secondary to  $\beta$ -lactam antibiotics and sulfa drugs, may be associated with fever, eosinophilia and rash. Renal manifestations include sterile pyuria, eosinophiluria, and an inflammatory infiltrate in renal interstitium on the biopsy. Reactions are generally idiosyncratic, and

management involves removal of the suspected causative agent and supportive therapy. Treatment with prednisolone 1mg/kg/day for up to 4 weeks may accelerate the rate of recovery<sup>53,54</sup>.

*Radiocontrast nephrotoxicity*

Iodinated contrast media are commonly used during the diagnostic workup of critically ill patients. AKI is a well recognized complication of contrast media resulting in increased in hospital mortality, prolonged hospital stay and increased health care costs<sup>55,56</sup>. The most important risk factor for developing AKI following contrast administration is the baseline glomerular filtration rate (GFR), with increased risk of AKI below estimated GFR of 60ml/min. Other risk factors include diabetes mellitus, heart failure, volume depletion, nephrotoxic drugs, and haemodynamic instability.

The volume and type of contrast media administered influence the risk of contrast nephropathy in critically ill patients. The volume of contrast medium administered correlates with nephrotoxicity<sup>57-59</sup>. The use of isosmolar (approximately 290 mOsm/kg) contrast media is associated with considerably less nephrotoxicity compared to low (500-800 mOsm/kg) and high osmolar contrast media<sup>60,61</sup>. Volume expansion prior to administration of contrast, preferably with isotonic fluids prevents contrast nephropathy. Intravenous fluid administration is likely to be preferable to oral hydration<sup>62</sup>. Isotonic fluids, (in particular normal saline) are preferable to hypotonic fluid resuscitation in the prevention of AKI<sup>63</sup>.

Although N-acetylcysteine (NAC) has been widely suggested to be of benefit, its beneficial effects have not been consistently seen. A recent meta-analysis showed that significant heterogeneity in NAC effect existed across studies, and that overall, no benefit was seen<sup>64</sup>. NAC is known to reduce serum creatinine (by activating creatinine kinase activity and possibly reducing tubular secretion) without improving GFR, and this effect may confound the results of clinical trials of its use in preventing contrast induced kidney injury<sup>65</sup>. The value of NAC in preventing

contrast nephropathy clearly needs further study, in view of the wide heterogeneity of effect shown in the different studies<sup>64</sup>. However given its relatively low incidence of side effects and low cost, together with evidence of benefit, current practice favours its use in addition to hydration in high risk patients receiving contrast.

Other pharmacologic agents suggested to be of benefit include theophylline, statins, ascorbic acid, and prostaglandin E1. Fenoldapam, dopamine, calcium channel blockers, atrial natriuretic peptide, and L-arginine have been shown to be ineffective. Theophylline shows some promise<sup>66</sup>. Furosemide, mannitol, and an endothelin-receptor antagonists are potentially detrimental<sup>67</sup>. The place of dialysis needs further study<sup>68</sup>, with no current evidence of preventive benefit in contrast nephropathy.

#### *The role of loop diuretics*

Despite some evidence from in-vitro studies that furosemide causes reduced expression of certain inflammatory mediators, there is no evidence that loop diuretics are of benefit in prevention or treatment of sepsis-induced AKI. Oliguric AKI, is associated with increased mortality compared to non-oliguric AKI<sup>69, 70</sup>. Hence clinicians often use loop diuretics to convert oliguric AKI to non-oliguric AKI<sup>71,72</sup>. Trial evidence however suggests that furosemide may actually increase the risk of death/ non-recovery of renal function<sup>71,72</sup> and two recent systematic reviews and a meta-analysis showed that loop diuretics are of no benefit in AKI<sup>73-75</sup>.

#### *The role of osmotic diuretics – mannitol*

It has been suggested that mannitol attenuates renal damage in animal models, increases renal blood flow and acts as a free radical scavenger preventing reperfusion injury of the kidney<sup>76</sup>. In practice however, the use of mannitol in patients with mild to moderate renal insufficiency was shown to be associated with greater risk of AKI when compared with saline alone<sup>77,78</sup>. Thus the use of mannitol should be discouraged.

#### *Insulin and tight glycaemic control*

Although tight glycaemic control was thought to reduce mortality in critically ill patients, current evidence is to the contrary- a recent meta-analysis showed a high incidence of hypoglycaemic events, with no evidence of mortality benefit<sup>79</sup>. However, tight glycaemic control using insulin in critically ill patients has been shown to be reno-protective, preventing oliguria and reducing the need for RRT<sup>80</sup>. The anti-inflammatory action of insulin may play a role in this effect. Further evidence is awaited.

#### **Conclusions**

Renal replacement therapy is the mainstay of management of sepsis induced acute renal failure. An adequate dose of dialysis is likely to improve outcome, though currently no consensus is available on the ideal dose, frequency or modality. Prevention of drug induced and contrast induced nephropathy is of great importance. Adequate volume resuscitation and the use of the correct inotrope are also important. Many other therapies have been tried, without clear benefit. Much controversy exists on many of these issues, and current evidence supports the concept that management of sepsis induced AKI should be fine tuned to the individual patient.

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