Dialytic Treatment for Septic Patients with Acute Kidney Injury

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Key Words

Sepsis · Acute kidney injury · Haemodialysis · Continuous renal replacement therapy · Haemofiltration · Bio-artificial kidney

Abstract

Background: Sepsis is the commonest precipitating factor for acute kidney injury in hospitalised patients, and similarly patients with acute kidney injury are predisposed to sepsis. Mortality remains high despite improvements in supportive care. **Methods:** Literature search of Medline and Web of Science. **Results:** Above a threshold dialytic dose of 20 ml/kg/h for continuous renal replacement therapy and a sessional Kt/V of 1.2 for intermittent dialysis, further increases in dose do not appear to impact on survival. Similarly, no treatment mode offers survival advantage, and renal support should be targeted to maintain electrolyte homeostasis and correct volume overload. Additional therapies designed to reduce the inflammatory milieu associated with sepsis have been studied, including increased permeability dialysers, plasma filtration and adsorption techniques, endotoxin filters, selective leucapheresis and bio-artificial renal devices. Antibiotic-coated catheters have been shown to reduce catheter-associated bacteraemia. **Conclusions:** Although no modality confers survival advantage, prevention of intratreatment hypotension may result in increased dialysis independence in the survivors, and as such treatments should be designed to minimise the risk of hypotension. As patients with acute kidney injury are at risk of sepsis, catheter-associated bacteraemia should be minimised by using antibiotic- or antiseptic-

coated catheters, and hub colonisation reduced with appropriate catheter locks. Further trials of adjunct therapies designed to reduce the inflammatory milieu are required before these potential advances can be recommended for clinical practice.

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Introduction

Sepsis probably is the commonest precipitating factor for acute kidney injury (AKI) in hospital practice, present in around 30% of patients developing AKI. Similarly patients with AKI are predisposed to sepsis, which subsequently develops in about 40% [1]. Mortality of patients with AKI complicated by sepsis remains around 40% in large studies from both North America [1] and Japan [2]. Both in-patient mortality is increased as well as post-discharge mortality and the survivors have longer intensive care and hospital in-patient stays [3].

Whether sepsis is localised or systemic, the inflammatory milieu which develops due to the systemic inflammatory response syndrome or the host compensatory anti-inflammatory response syndrome has local effects as well as systemic consequences including confusion [4], cardiac depression, activation of coagulation cascades and fibrinolysis, and AKI.

As such, renal dialytic support centres on dialysing patients at increased risk of hypotension, access and extracorporeal circuit thrombosis and on trying to modify the inflammatory milieu.

Fig. 1. Early changes in mean arterial blood pressure and systemic vascular resistance in patients with sepsis and AKI treated by sham continuous venovenous haemofiltration. Figures are means and SEM. * $p < 0.05$ vs. before haemofiltration (data are courtesy of Dr. P. Johnson).

Preparing the Dialysis Machine

Intradialytic hypotension is commonly encountered in chronic haemodialysis patients attending routine haemodialysis sessions [5], and is typically due to a combination of high ultrafiltration rates, that do not allow compensatory refill of the intravascular compartment, and patient comorbidities [6]. However, septic patients with AKI are much more susceptible to intradialytic hypotension due to systemic vasodilatation, coupled with a cardiac output which, although increased, is suboptimal for the degree of vasodilatation due to the presence of cardiodepressant factors. As part of the inflammatory milieu background, plasma concentrations of nitric oxide and bradykinin are increased with increased complement activation [7]. At the start of the dialysis, the passage of dilute blood across the dialyser can generate bradykinin and the anaphylatoxins C3a and C5a. Increased bradykinin and C3a/C5a production can lead to hypotension. In the chronic dialysis patients, this reaction with the extracorporeal circuit is greater for patients prescribed angiotensin-converting enzyme inhibitors, which prevent bradykinin degradation, dialyser membranes with negatively charged surfaces, use of heparins which have increased negative charge, priming the circuit with normal saline or blood due to the negatively charged chloride or citrate, respectively, and endotoxin- or peptidoglycan-contaminated dialysate. However, in the patients with systemic sepsis, bradykinin generation

is more dependent upon the severity of the systemic inflammatory response syndrome response rather than dialyser choice [7]. Even so, the risk of early hypotension during treatment (fig. 1) can be reduced by rinsing and priming the circuit with isotonic bicarbonate, and using either no anticoagulation or minimising heparin exposure by administering heparin into the venous limb of the circuit.

Dose of Dialysis for Patients with Sepsis and AKI

Although it is accepted that the dose of haemodialysis delivered is important for chronic dialysis patients, a threshold dose has not been established for patients with AKI [8]. In AKI, nitrogenous waste products rapidly accumulate, but carbamylation, whereby urea dissociates to cyanate and then reacts with proteins and lipoproteins, takes 8–12 days [9]. As such, volume overload and electrolyte imbalances are more likely to lead to patient morbidity and mortality in the first week of AKI than uraemic solutes.

However, previous studies on AKI reported a benefit of an increased delivered dose of dialysis, when compared to a low dose (Kt/V of <0.9) [10], and in particular a survival advantage for patients with sepsis [11], although later multicentre studies, which recruited between 30 and 50% of patients with sepsis, did not show any benefit above a delivered haemodialysis target Kt/V of 1.2 [12] or an effluent volume of 25 ml/kg/h for continuous renal replacement therapy (CRRT) [13]. Compared to the earlier study which reported a survival advantage for septic AKI patients treated with CRRT delivered at a dose of 45 ml/kg/day [11], the other studies delivered lower CRRT doses due to increased CRRT circuit clotting (prescribed 40 ml/kg/h vs. delivered 33 ml/kg/h) [12]. Thus, although above a critical dose of renal replacement therapy ($Kt/V \geq 1.2$ for haemodialysis, and 20 ml/kg/h for CRRT) there does not appear to be a survival advantage for higher dosages, the recent multicentre studies failed to deliver the doses of the earlier Ronco study [11].

Frequency

In the intensive care setting, patients may be given several litres of fluid a day, in the form of vasopressor, antibiotic and other infusions, and nutrition, thus potentially increasing the ultrafiltration requirements for intermittent dialysis. Initial studies reported a lower in-

Table 1. Different available modalities for treating AKI

Modality	CVVH	CVVHD	CVHDF	PD	PIRRT	IHD
Qb, ml/min	100–250	100–250	100–250	none	100–300	200–350
Qd, ml/min	none	25–50	25–50	25–42	200–300	300–800
Therapy time, h	24	24	24	24	6–12	4–6
Solute transport	convection	diffusion	diffusion convection	diffusion	diffusion	diffusion
Ultrafiltrate, l/h	1.5–3.0	variable	1.5–3.0	variable	variable	variable
Effluent volume, l/day	36–72	36–72	36–72	36–60	variable	variable
Replacement fluid, l/h	1.5–3.0	none	1.5–3.0	none	none	none
Urea clearance, ml/min	20–40	25–45	25–45	15–35	90–140	150–180

CVVH = Continuous venovenous haemofiltration; CVVD = continuous venovenous haemodialysis; CVVHDF = continuous haemodiafiltration; PD = peritoneal dialysis; PIRRT = prolonged intermittent renal replacement therapy; IHD = intermittent haemodialysis; Qb = blood flow; Qd = dialysate flow.

cidence of intradialytic hypotension with daily therapies compared to standard thrice-weekly haemodialysis [11]. However, in the Veterans/NIH study, intradialytic hypotension paradoxically was more commonly observed in the more frequent haemodialysis group [12]. This was due to increased fluid administration and therefore higher ultrafiltration rates in this group. Thus, intensivists should carefully review fluid administration in critically ill patients to reduce the ultrafiltration requirements during dialytic therapies, and as volume overload is associated with increased risk of mortality [14], more frequent treatments are required to prevent volume overload.

Mode of Renal Replacement Therapy

The options for treating patients with AKI have expanded from peritoneal and haemodialysis, to include intermittent haemofiltration/haemodiafiltration, continuous haemofiltration/haemodiafiltration and prolonged intermittent renal replacement therapy [15], formerly termed slow extended daily dialysis (table 1). Although haemofiltration techniques increase middle molecular weight solute clearances compared to dialysis-based modalities, which predominantly rely on diffusive clearance, no studies have shown a clinical benefit when treating patients with AKI. In prospective trials, CRRT has been shown to improve patient survival following AKI compared to peritoneal dialysis [16], although the delivered dose of peritoneal dialysis was much lower than that for CRRT [17]. In other retrospective and prospective studies, continuous

Fig. 2. Changes in cerebral perfusion pressure in patients with acute failure and endotoxaemia treated by continuous venovenous haemofiltration (CVVH) and pulse HVHF using warmed replacement fluid. Pulse HVHF stopped after 240 min. Figures are means and SEM.

modalities have not shown any superiority compared to intermittent techniques. However, in all these studies, the most critically ill patients were excluded from randomisation, and were typically treated with CRRT [17]. Thus for cardiovascularly stable patients, no treatment modality appears to be superior, as there are advantages and disadvantages for each modality (table 2). However, for patients with AKI, particularly those with cerebral oedema and cardiovascular instability, CRRT offers an advantage to standard intermittent techniques (fig. 2).

Table 2. Theoretical advantages and disadvantages of different renal replacement modalities

Modality	Potential role	Advantages	Disadvantages
PD	<ul style="list-style-type: none"> – Paediatrics – Single organ failure – Haemodynamically unstable patients – Coagulopathy – Difficult vascular access 	<ul style="list-style-type: none"> – Technically simple – No anticoagulation – Gradual removal of azotaemic toxins – Usually haemodynamically stable – Lower financial costs 	<ul style="list-style-type: none"> – Low clearances in patients with reduced mesenteric blood flow – Unpredictable fluid removal Intact peritoneum – Required – Risk of peritonitis hyperglycaemia, and hypostatic pneumonia
CRRT	<ul style="list-style-type: none"> – Haemodynamically unstable patients – Patients at risk of raised intracranial pressure 	<ul style="list-style-type: none"> – Continuous removal of azotaemic toxins – Haemodynamic and intracranial stability – Reliable volume control 	<ul style="list-style-type: none"> – Slower clearance of toxins and poisons – Prolonged anticoagulation – Immobilization – Hypothermia – Financial costs
PIRRT	<ul style="list-style-type: none"> – Haemodynamically unstable patients – General ICU patients with AKI 	<ul style="list-style-type: none"> – Faster removal of azotaemic toxins than CRRT, but slower than IHD – More haemodynamically stable than IHD – Reduced exposure to anti-coagulation allows time for diagnostic/therapeutic procedures and reduces immobility 	<ul style="list-style-type: none"> – Slower clearance of toxins and poisons than IHD – Requires ultrapure dialysate and anticoagulation
IHD	<ul style="list-style-type: none"> – Haemodynamically stable patients 	<ul style="list-style-type: none"> – Rapid removal of azotaemic toxins and poisons allows time for diagnostic/therapeutic procedures – Reduces immobility – Reduced anticoagulation requirements – Lower financial costs 	<ul style="list-style-type: none"> – Increased risk of hypotension, and dialysis disequilibrium with intracranial hypertension

PD = Peritoneal dialysis; PIRRT = prolonged intermittent renal replacement therapy; IHD = intermittent haemodialysis.

Does the Choice of Dialyser Impact on Outcome in Patients with AKI?

Dialyser design and membrane composition have changed markedly over the last 30 years, with the development of synthetic polymer compositions designed to increase internal filtration and reduce bio-incompatibility [18]. Early studies comparing unmodified cellulosic dialysers with synthetic dialysers reported an advantage for septic patients, both in terms of recovery of residual renal function as well as patient survival. However, later studies and meta-analyses did not show any overall benefit of synthetic membranes compared to those made from modified cellulose, although in critically ill patients with cardiovascular instability membrane reactions can cause hypotension [19]. Studies of low-flux dialysers compared to high-flux dialysers made from the same polymer did not show any advantage for high-flux dialysers.

High Cut-Off Dialysers

The greater the inflammatory response during AKI, the greater the risk of mortality, irrespective of whether the host response is predominantly pro-inflammatory (e.g. high levels of IL-6) or predominantly anti-inflammatory (e.g. high levels of IL-12). Although haemofiltration modes would be expected to remove larger solutes, more cytokine removal was shown to be due to membrane adsorption than ultrafiltration [20], as some cytokines such as tumour necrosis factor exist in plasma as trimers, and others bind to proteins and heparin. To increase cytokine removal, a new generation of dialysers was developed, termed high cut-off dialysers. Although these dialysers have been shown to increase cytokine and other inflammatory mediator clearances compared to conventional dialyser membranes [21], they have not been shown to improve patient survival or reduce the duration of AKI.

Plasma Exchange and Separation Techniques

Several small case series from single centres reported survival advantage for septic patients with AKI treated with plasma exchange, particularly in paediatric practice with meningococcal septicaemia. However, these exciting results could not be replicated in prospective trials. As plasma exchange is limited to 30–40 ml/kg, combination therapies were developed to provide plasma exchange coupled with adsorption, whereby the filtered plasma was passed through charcoal, resin or ion exchange columns. One of these devices, termed coupled plasma filtration adsorption, was shown to both attenuate hypotension associated with septic shock as well as to dramatically improve the immunoparalytic toxicity of septic plasma. Monocytes from patients treated with coupled plasma filtration adsorption underwent a major improvement in their ability to respond to endotoxin [22]. Further clinical trials are awaited to determine whether these techniques improve clinical outcomes in terms of patient survival and recovery from AKI.

Endotoxin Filters

Endotoxin filters were developed to improve dialysate water quality and allow haemodialysis and haemodiafiltration to be provided to intensive care units without the benefit of a treated water plant. As endotoxin levels are increased in patients with AKI, secondary to a breakdown of the gastro-intestinal barrier and reduced hepatic Kupfer cell uptake, extracorporeal circuits using endotoxin filters were introduced into the treatment of patients with sepsis [23]. Although endotoxin filters have been used for many years in Japan, a recent multicentre European trial used polymyxin B endotoxin filters in the treatment of patients with intra-abdominal sepsis, which was reported to improve 28-day survival. However, there was no difference in AKI between the groups; if anything, more patients developed AKI in the endotoxin filter-treated group [23].

Bio-Artificial Devices

Bio-artificial kidney devices have been developed using capillary dialysers coated with animal or human proximal tubular cells. These cells retain their polarisation and not only transport characteristics but also endocrine and metabolic functions, including protein and peptide uptake and degradation. A recent phase II study

reported not only on the safety of such devices, but also observed improved survival and resolution of AKI in a group of patients with multiple organ failure [24].

An alternative approach for patients with multiple organ failure and severe sepsis has been to develop a device designed to remove activated inflammatory cells. Leucapheretic devices have been developed which can bind and selectively reduce leucocyte activation and are currently undergoing early clinical trials.

High-Volume Haemofiltration

High-volume haemofiltration (HVHF) has been a technique used for more than a decade, but it is only more recently, following the technological improvements with haemofiltration machines, that this treatment has become safer and easier to perform and is currently defined as either achieving ultrafiltration rates of 50–70 ml/kg/h for 24 h, or pulses of higher volumes of 100–120 ml/kg/h for 4–8 h (pulse HVHF).

Initial animal studies reported that HVHF resulted in improved haemodynamics in animals with septic shock, and importantly ultrafiltrate from these animals caused hypotension when injected into healthy animals, suggesting that HVHF was having an effect by removing inflammatory mediators. These beneficial effects of HVHF were similarly reported in small series of patients with multiple organ failure [25]. Several single centres then reported markedly improved survival with HVHF, but unfortunately in the randomised IVOIRE trial, the group randomised to HVHF had similar outcomes. However, HVHF has been shown to improve patient outcomes following randomised trials in patients after cardiac arrest [25].

Although HVHF has been advocated to reduce inflammatory mediators and allow a resetting of the balance between systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome, high-volume exchanges also increase nutrient and trace element losses on the one hand, and antibiotic clearances on the other. This has led to the development of pulse HVHF to allow for nutritional support and antibiotic dosing to be tailored around the pulses of HVHF.

Prevention of Hypotension and Recovery from AKI

It has been suggested that repeated episodes of intra-dialytic hypotension may delay recovery from AKI and increase the risk of dialysis dependence [17]. When CRRT

was first introduced, intermittent haemodialysis in the intensive care unit centred on machines without accurate ultrafiltration control, unmodified cellulosic membrane dialysers, and warmed acetate-based dialysate. Just as there have been many improvements in CRRT over the last 30 years, intradialytic hypotension can be reduced by not only lengthening dialysis sessions and increasing the frequency of treatments to reduce ultrafiltration requirements, but also by using bicarbonate-based dialysates coupled with higher dialysate sodium [26] and reducing dialysate temperature [27]. Although haemodiafiltration was initially reported to reduce intradialytic hypotension compared to haemodialysis, this was subsequently shown to be due to additional cooling, particularly with the predilutional mode, and when patients were equally cooled there was no difference between modes [28]. This effect of cooling may in part explain some of the cardiovascular stability observed with HVHF.

Anticoagulation

Patients with AKI and sepsis typically have increased platelet, leucocyte and coagulation cascade activation but also fibrinolysis. As such, clotting in extracorporeal circuits and access catheters is more common. Heparin may not be as effective an anticoagulant as many septic AKI patients have reduced antithrombin levels. For CRRT to be effective, circuits must be continuous, and this has led to the renewed interest in citrate anticoagulation, particularly as citrate is essentially a regional rather than a systemic anticoagulant. As citrate chelates calcium, there have been differing reports as to whether citrate reduces leucocyte and platelet function, and some reports of increased patient survival with citrate anticoagulation compared to heparin. However, a recent multicentre prospective trial reported no survival benefit [29].

Dialysis Access Catheters

Sepsis often develops in patients with AKI [1], and venous access catheter bacterial colonisation and associated bacteraemia are well recognised in the intensive care setting. It is therefore important to reduce the risk of catheter-associated infection. The introduction of antibiotic and antiseptic catheter locks can reduce the incidence of nosocomial hub infections. However, as catheter locks are lost from the catheter tip, particularly in catheters with side holes [30], citrate and taurolidine locks tend to

lead to increased catheter thrombosis than combinations of antibiotics and heparin. In addition, the introduction of antibiotic- or silver-impregnated catheters has also reduced the incidence of catheter-associated bacteraemia by reducing periluminal spread [31].

Conclusion

The mortality of patients with sepsis and AKI remains high. Sepsis is a common precipitating factor for AKI in the hospital setting, and also often complicates AKI. Dialytic support centres on supportive care, designed to maintain electrolyte homeostasis, correct volume overload and prevent azotaemia. Currently no treatment modality appears to be superior, although clearances with peritoneal dialysis are less than those of other techniques. Although CRRT offers improved cardiovascular stability, this has not resulted in improved patient survival, although prevention of intratreatment hypotension may potentially lead to greater dialysis independence in survivors.

Additional approaches designed to reduce the inflammatory milieu of the septic patient with AKI, including highly permeable dialysers, plasma separation coupled with adsorption, endotoxin absorption, HVHF and bio-artificial and leucopheretic devices remain to be proven.

Disclosure Statement

The author has no conflict of interest.

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