Acute kidney injury in sepsis

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Abstract

Sepsis is life-threatening organ dysfunction resulting from a dysregulated host response to infection. It is one of the commonest causes of acute kidney injury (AKI) and is associated with an increase in both morbidity and mortality. Both haemodynamic and non-haemodynamic factors are involved in the pathogenesis of AKI in sepsis. Newer tests are available for the early diagnosis of AKI in septic patients and may provide an opportunity for prevention. The current mainstay of prevention is adequate fluid resuscitation and maintenance of systemic blood pressure, noradrenaline being the vasopressor of choice. Renal replacement therapy may improve outcomes. Continuous renal replacement modalities are preferred in those who are haemodynamically unstable. There is no consensus on the optimal timing or dose of renal replacement therapy.

Introduction

Sepsis has recently been redefined as life-threatening organ dysfunction resulting from a dysregulated host response to infection [1]. Renal dysfunction may be seen in up to 16-67% of patients with sepsis [2]. This manifests as acute kidney injury (AKI), and is diagnosed based on a rise in serum creatinine and/or a reduction in urine output within a short period of time [3]. Sepsis is one of the commonest causes of AKI, and accounts for 26-60% of AKI seen in developed nations [2].

The occurrence of AKI in a patient with sepsis is a bad prognostic factor and is associated with increases in patient morbidity and mortality, as well as in health care costs [4].

Pathophysiology of AKI in sepsis

The pathogenesis of AKI in sepsis is poorly understood. This may be one of the reasons why the outcomes of sepsis-induced AKI remain unsatisfactory, even in the face of medical advancement.

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The classical models of pathophysiology have concentrated on sepsis induced haemodynamic changes as being the main mechanism of kidney injury in sepsis. However, more recent understanding is that both haemodynamic and non-haemodynamic mechanisms contribute to the development of AKI in septic patients. [5, 6] Difficulties in performing invasive experimental tests on critically ill patients and the lack of comparable animal models have hindered attempts to gain information about human sepsis-induced AKI. Much of our current understanding is based on limited human studies or indirect evidence from conflicting animal studies [5].

a) Haemodynamic changes in sepsis and AKI

The haemodynamic effects of sepsis on the kidney are variable. On one hand some studies have shown that endotoxaemia results in a reduction in renal blood flow and, hence, glomerular filtration rate. This hypoperfusion, if prolonged, can lead to tubular ischemia and acute tubular necrosis [7]. However, other studies have shown that the renal circulation participates in the systemic vasodilatation that is seen in sepsis, thereby leading to increased renal blood flow and the occurrence of AKI in a setting of normal or increased renal perfusion [5, 8].

This underscores the importance of glomerular filtration pressure, rather than renal blood flow, as a major determinant of glomerular filtration rate and kidney function. Glomerular filtration pressure is determined by the balance between the vascular tone of the afferent and efferent arterioles of the glomerulus. In the presence of both afferent and efferent arteriolar dilatation, with the efferent affected more than the afferent the glomerular filtration pressure will fall, despite an increase in renal blood flow. This may set the stage for hyperdynamic AKI, a unique form of AKI that is seen in sepsis [5].

How far these models, which are mainly based on animal studies, truly reflect the pathogenesis of human AKI is still open for debate. Further studies on humans will be needed to test their validity.

b) Non- haemodynamic injury leading to AKI in sepsis

Neither global nor intra-renal haemodynamic changes have

been consistently shown to be the sole contributor to the development of AKI in sepsis. The non-haemodynamic factors contributing to sepsis induced AKI may be immunological or toxic. A multitude of inflammatory mediators and neuroendocrine mechanisms play a role in the response to infection [9].

The reaction to severe infection comprises a pro-inflammatory and an anti-inflammatory response, which are activated in sequence and may sometimes overlap. [10] The recognition of pathogen associated molecular patterns (PAMPs) by Toll like receptors (TLR) on innate immune cells leads to activation of the humoral and cellular arms of the innate immune response. This results in the activation of complement and procoagulatory pathways, recruitment of inflammatory cells, release of pro-inflammatory cytokines, and formation of free radicals. These humoral and cellular changes result in widespread endothelial dysfunction, capillary leakage, microvascular thrombosis and impaired vascular tone. At the level of the kidney this manifests as infiltration of the renal parenchyma with inflammatory cells, intra-glomerular thrombus formation, and obstruction of the renal tubules with necrotic cells and debris [6]. Apoptosis of renal tubular cells and tubular dysfunction in the face of sepsis may contribute to kidney injury and the development of acute renal failure [5].

Detection of AKI in sepsis

Early detection of AKI in sepsis may allow for therapeutic measures that will improve outcomes. The detection of AKI by current diagnostic criteria based on serum creatinine and reduction in urine output may be delayed, and may therefore reduce the effectiveness of therapeutic interventions.

In fact, due to a variety of reasons, serum creatinine is an unreliable marker in diagnosing AKI in patients with ongoing sepsis [11,12]. Certain novel biomarkers may be better predictors of AKI. These include urinary interleukin-18 (IL-18)[13], neutrophil gelatinase associated lipocalin (NGAL) [14] and kidney injury molecule-1 (KIM-1)[15]. Interestingly, some of these biomarkers are noted to be higher in sepsis associated AKI compared to non-septic AKI.[6] However the exact role of these biomarkers in the diagnosis of AKI in the setting of sepsis is not yet clearly defined and therefore they are not yet recommended for routine use in the ICU.

Prevention and management of sepsis induced AKI

a) Fluid resuscitation and vasopressors

Controversy remains regarding the effectiveness, type, volume and duration of fluid resuscitation in septic shock [16]. Contrary to traditional teaching, the principle that more is better is no longer true, even with regard to the kidney. Though volume resuscitation is vital to maintain cardiac output, over-hydration results in tissue oedema and a reduction in oxygen delivery to target tissue. Low plasma oncotic pressure seen as part of the systemic response to inflammation, exacerbates tissue oedema in fluid overloaded patients [17]. While early aggressive fluid resuscitation may be life- saving, it may be necessary to combine this with early initiation of renal replacement therapy to in order to avoid fluid overload [16].

Crystalloids are preferred over colloids in fluid replacement. In particular hydroxyl ethyl starch (HES) has been associated with osmotic nephrosis and is best avoided [18]. Among the crystalloids buffered solutions such as Ringer's lactate may have benefits over isotonic saline [19]. Sepsis guidelines advocate a central venous pressure of 8-12 cmH_20 to be maintained in septic patients[20]. High central venous pressure may be detrimental to renal function as tissue oedema within the renal capsule may result in a "renal compartment syndrome" leading to a reduction in effective renal perfusion and, therefore, function [16]. The target mean arterial pressure in sepsis as recommended by guidelines is 65 mmHg [20].

The vasopressor of choice is noradrenaline, as kidney performance in sepsis is dependent on renal perfusion pressure rather than renal oxygen delivery [21]. This is despite previous concerns that vasoconstriction may aggravate renal hypoperfusion, a theory that has since been proven false. In fact renal perfusion has been shown to increase with norepinephrine, perhaps due to an increase in the mean arterial pressure as well as reflex renal vasodilatation following the increase in systemic blood pressure [22]. Concerns regarding the use of adrenaline include the risk of tachycardia, hyperglycaemia, hyperlactataemia and acidosis. There is no place for "low dose" dopamine as a reno-protective inotrope [23].

b) Supportive management

Diuretics

Diuretics may be beneficial in patients with evidence of fluid overload. They should not be used for the sole purpose of improving urine output, particularly in hypovolemic patients [16].

Avoid nephrotoxins

Drugs to avoid in AKI include angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs), and radiocontrast. All drug doses and dosing regimes, including those of antibiotics, must be adjusted according to the estimated glomerular filtration rate and the Renal Replacement Therapy (RRT) modality and time schedule.

c) Renal replacement therapy

The goals of renal replacement therapy (RRT) in AKI are to optimize fluid and electrolyte, acid-base, and solute balance, prevent further renal injury while promoting renal recovery, and to allow other supportive measures, such as drug therapy and nutrition, to proceed with minimal limitation [3].

Modalities of RRT

The main modes of RRT in acute kidney injury can be broadly categorized as intermittent and continuous. Intermittent RRT includes intermittent haemodialysis and isolated ultrafiltration delivered in short intermittent courses separated by several hours or days. This contrasts with continuous therapies which are, by their very definition, uninterrupted. The continuous therapies include continuous venovenous haemodialysis (CVVHD), continuous venovenous haemodiafiltration (CVVHDF) and continuous venovenous haemofiltration (CVVHF) which are based on varying combinations of the principles of diffusion, ultrafiltration and convection. Intermittent RRT is often more readily available, less expensive, allows for more rapid correction of fluid and electrolyte imbalances and maintains the mobility of the patient while off treatment. However, CRRT has the advantage of causing less haemodynamic disturbance and allowing for smoother fluid management, at the cost of risks such as prolonged anticoagulation.

Guidelines recommend that haemodynamically unstable patients are best managed with continuous renal replacement therapies (CRRT). There is, as yet, no evidence to recommend either CRRT or intermittent renal replacement therapies (IRRT), such as haemodialysis, over the other in haemodynamically stable patients [3]. Hybrid methods such as slow low efficiency daily dialysis (SLEDD) attempt to combine the best of both intermittent and continuous therapies while minimizing their disadvantages.

Timing of RRT

Absolute indications to initiate RRT are severe hyperkalaemia, severe acidosis, pulmonary oedema, and uraemic complications [3, 24]. There may be benefit in initiating CRRT at the onset of kidney injury before frank conventional clinical and biochemical criteria are met [25]. However, the evidence for this approach is conflicting and studies have not consistently shown any advantage in early initiation of RRT [3]. Clinicians often observe clinical and biochemical trends in making decisions on RRT.

Dose of RRT

Uncertainties remain regarding the optimal dosing of RRT in AKI. The Acute Renal Failure Trial Network (ARFTN) study demonstrated that there is no benefit of intermittent haemodialysis six times a week vs three times a week or CVVHDF at a dose of 35 ml/kg/h vs 20 ml/kg/h [26]. Similarly The Randomized Evaluation of Normal versus Augmented Level (RENAL) replacement therapy study failed to show any advantage of 40 ml/kg/h CVVHDF vs 20 ml/kg/h [27].

Potential therapies

Potential therapies for sepsis induced AKI may focus on targeting the inter-connected pathogenetic mechanisms of inflammation, microvascular dysfunction and tubular cell adaptation. Studies based on the importance of cytokines in this process have offered haemadsorption as a potential strategy to prevent the onset of AKI in sepsis[28]. Extracorporeal therapy with Polymixin B has been shown in some clinical studies to reduce pro-apoptotic factors leading to kidney injury and to reduce organ dysfunction in sepsis [29,30]. Adjunctive treatment with exogenous alkaline phosphatase is currently under investigation for its detoxifying potential [16].

Conclusion

The development of AKI in sepsis is a consequence of systemic and local haemodynamic changes that result in reduced glomerular filtration and non – haemodynamic toxic and immunological processes. Present tactics in treatment and prevention focus largely on correcting the haemodynamic changes of sepsis. These include fluid resuscitation and vasopressors.

The initiation of renal replacement therapy is known to improve outcome, though the timing, intensity and mode are still under debate. CRRT is preferred in haemodynamically unstable patients. Treatment varies according to the individual patient. The future may lead to therapies that directly target the inflammatory pathways that lead to sepsis offering an opportunity for further prevention of AKI in sepsis.

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