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Review

Management of acute kidney injury in sepsis

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ABSTRACT

Acute kidney injury and multiorgan dysfunction due to sepsis and septic shock increase the morbidity and mortality among critically ill patients. It remains an important challenge in critically ill patients. In this review, management of septic AKI in terms of prevention, medical therapies, and extracorporeal therapies is discussed. Stabilizing the hemodynamic parameters by fluid resuscitation and inotropic support are important strategies to prevent acute kidney injury in the initial stages. Controversies exist in the timing of initiating renal replacement therapy although some studies showed improved outcomes with early initiation. The recommended dose of renal replacement therapy (25 ml/kg/hr) had not shown to be associated with improved survival in randomized studies. The clinical benefit of other therapies, like hemoadsorption, and alkaline phosphatase use is still uncertain. Mesenchymal stem cell therapies are in phase I trials.

1. Background

Multiorgan failure due to sepsis and septic shock is one of the most common causes of increase in mortality and morbidity in critically ill patients. The development of new onset organ failure in intensive units is associated with increase in mortality.[1] Acute kidney injury due to sepsis develops in critically ill patients as a part of multiorgan dysfunction and is associated with significant increase in morbidity and mortality. It also increases the cost of intensive unit care stay. The overall incidence of sepsis-associated acute kidney injury in intensive unit admission is reported to be 15–20%.[2] In some of the studies, the incidence of septic AKI approaches to around 50%.[3,4] Mortality also increases with development of sepsis-associated acute kidney injury. The IVOIRE study had shown 90-day mortality rate of 50% in sepsis-associated acute kidney injury patients.[5]

The main management of septic acute kidney injury revolves around treating the underlying sepsis with appropriate antibiotics and supporting the organs till the sepsis is managed. So, the acute kidney injury in sepsis is managed by achieving adequate hemodynamic status by intravenous fluids or inotropic support and then if needed by extracorporeal blood purification. In this review, we will discuss about the preventive and treatment aspects of sepsis-associated acute kidney injury.

2. Preventive strategies

2.1. Fluid resuscitation

The main initial strategies in the management of septic shock and septic acute kidney injury are maintaining the hemodynamic parameters by either fluid therapy or by inotropes. Acute kidney injury due to sepsis is due to regional hypoperfusion of kidney leading to ischemia-reperfusion damage and is also related due to the effect of toxins and cytokines. Renal tissue can be further damaged by the use of nephrotoxic drugs, use of contrast agents, and associated comorbidities with the patient.

Improving the hemodynamic status of the patient will lead to improvement in renal perfusion. In patients with sepsis and septic shock, fluid should be administered liberally after evaluating the cardiac status and it should be stopped when cardiac output reaches normal value. Fluid therapy can act as a double-edged weapon because excessive fluid administration can have negative effects on organ function. The timing of stopping fluid therapy and starting renal replacement therapy is an area of controversy. Hence, the optimal fluid management is step-wise transition from initial unrestricted fluid administration to maintain neutral fluid balance to appropriate fluid removal when required.[6]

The surviving sepsis campaign guidelines mention that fluid resuscitation should be given in septic shock patients to maintain

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central venous pressure of 8–12 mmHg and mean arterial pressure of more than 65 mmHg.[7]

The early goal directed therapy (EGDT) for sepsis recommends starting fluids, vasopressors, and blood products to maintain central venous oxygen saturation of more than 70%.[8] This has been proved to improve survival in a cohort of sepsis with multiorgan failure patients. But recent studies did not show mortality benefit with this approach leading to controversies in fluid administration. Three main randomized studies (ARISE, ProMISe, and ProCESS) did not show survival benefit with EGDT approach.[9–11] In a retrospective study done by Kelm et al., fluid administration leading to fluid overload was associated with increased use of fluid-related medical interventions and mortality.[12]

2.2. Crystalloids versus colloids

To improve the hemodynamic status in septic AKI patients during the initial period, both crystalloids and colloid solution were used. But recent evidence suggests that crystalloid solutions rather than colloids should be used for initial resuscitation of patients with septic AKI,[13,14] the reason being the increased risk of osmotic nephrosis by colloid solutions.[15]

In crystalloids, balanced solutions (ringer lactate and plasmalyte) should be preferred over the isotonic solutions as the latter contains high chloride content, which produces vasoconstriction and is detrimental to the renal tissue.[16,17] This has been shown in some studies that isotonic solution was associated with increased morbidity and mortality. However, a recent, large randomized study (SPLIT) did not find any significant difference in incidence of AKI when comparing the two solutions. So, the superiority of balanced crystalloids yet remains to be proven.[18]

2.3. Albumin

The use of albumin infusion for resuscitation in septic shock patients had been studied in SAFE study.[19] This study and another meta-analysis showed that use of albumin was associated with lower mortality compared to other crystalloids.[20] In another recently published ALBIOS trial, mortality benefit with the use of albumin was not established.[21] In post-hoc analysis of this study, a subgroup of septic patients treated with albumin and crystalloid infusion had lower 90-day mortality compared to patients who were treated with crystalloids alone. Despite this, the use of albumin as resuscitation fluid is still under debate.

2.4. Use of inotropes

Inotropes are needed to maintain effective renal perfusion. In septic patients, noradrenaline seems to be the drug of choice.[22] Vasopressin is another drug that can be used in septic shock patients. Although mortality did not differ much between the use of these two inotropes, a post-hoc analysis of a trial done by Russell et al. found that in patients who developed milder forms of acute kidney injury, vasopressin use is associated with lesser progression to severe AKI than with noradrenaline.[23] In some studies, it was found that vasopressin use was associated with lesser progression to stage 1 AKI but not to severe stages.[24]

There is no definite evidence supporting or opposing the strategies for prevention of AKI in sepsis. To standardize treatment and optimize the timing, AKI should be diagnosed and monitored according to AKIN and KDIGO criteria.

2.5. Monitoring of progression

Recognizing AKI early and to determine the need for RRT can be done by various criteria that have been proposed to diagnose AKI. The RIFLE, AKIN, and KDIGO criteria are used to diagnose acute kidney injury.[25,26] But recent trial did not confirm improved outcomes by early diagnosis using these criteria.[27]

Oliguria is a useful earlier sign than serum creatinine in monitoring the progression in septic acute kidney injury.[28] Biomarkers like NGAL (neutrophil gelatinase-associated lipocalcin), tissue inhibitor of metalloproteinases, and urine insulin-like growth factor are useful in diagnosis of septic acute kidney injury.[29,30] But because of limited availability, these could not be used in routine clinical practice.[31]

2.6. Fluid overload and septic AKI

Positive fluid balance is associated with increased risk of development and progression of AKI.[32] The kidney tissue is affected by congestion and rise in renal venous pressure, which leads to reduction in blood flow and glomerular filtration. In a multicentre observational study done by Teixeira et al., in 601 critically ill patients, positive fluid balance and lower urine volume with AKI were associated with significant risk of 28-day mortality.[33] Many observational studies mention that net positive fluid balance is associated with increased risk of progression of AKI and mortality.[34–36] So removing fluid by either diuretic therapy or by extracorporeal therapy is essential to improve the beneficial effect of treatment of sepsis.

2.7. Diuretic therapy in sepsis and septic shock

Diuretic therapy is mainly used to increase the urine output and to maintain the neutral balance in fluid overload patients. Loop diuretics that act on medullary thick ascending limb of loop of Henle is the diuretic of choice. Theoretically, loop diuretics reduce the oxygen demand, maintain net fluid balance and acid–base homeostasis, and it should be helpful in reducing the severity of septic AKI. But most of the studies did not mention renal recovery and mortality benefit with diuretics.[37,38] Controversy still exists whether diuretic therapy improves outcomes in AKI with sepsis.[35,39]

The use of diuretics in absence of hypervolemia is associated with increased mortality and it should not be encouraged.[40]

Low-dose continuous diuretic infusion is found to be better in improving the urine output and reducing the BNP levels.[41] Diuretic resistance and adverse effects, such as metabolic disturbances, can occur with the use of diuretics. The main strategies while using loop diuretics is avoiding braking phenomenon and limiting its use to reduce side effects and resistance.

Use of fenoldapam in critically ill patients who are at risk of AKI was associated with reduction in degree of subsequent renal dysfunction.[42] But results of recent studies using fenoldapam had created controversy in using it in critically ill patients.[43] However, larger randomized trials are needed to evaluate the benefit of this drug in sepsis and septic shock.

3. Extracorporeal therapies

3.1. Indication and timing of RRT

If the medical therapy fails to maintain the fluid status, electrolyte, and acid–base balance, then renal replacement therapy should be initiated. Initiating renal replacement therapy aids the clinician in maintaining the fluid balance while providing adequate nutrition support through parenteral nutrition. It also helps to correct metabolic abnormalities associated with sepsis and decreased organ perfusion.

Early initiation of RRT is crucial and is found to be associated with better outcome in some studies. Delay in initiating the RRT is