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A synopsis on optimising fluid therapy in sepsis: challenges in resource-limited settings

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Abstract

Fluid therapy is a cornerstone of sepsis management, yet controversy surrounds several aspects of its administration. Optimising fluid therapy in sepsis requires a nuanced understanding of the underlying pathophysiology, patient-specific factors, and the latest evidence. This review summarises the current evidence on fluid therapy in sepsis, highlights challenges in low—and lower-middle-income countries (LMICs), and areas of future research (burden of sepsis, appropriate fluid management, role of care bundles, etc).

Keywords: Care bundles, Fluid therapy, Fluid responsiveness, Sepsis, Septic shock.

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1,2] It is an important cause of morbidity and mortality amongst critically ill patients globally, occurring in up to 40% of intensive care unit (ICU) admissions and with a mortality rate ranging from 11.9 – 39.5%.[1,3] Septic shock refers to a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to increase mortality substantially.[1] The terminology severe sepsis was used to describe sepsis complicated by organ dysfunction, but its use is now considered superfluous and has been abolished in the Sepsis-3 consensus definition.[1]

Sepsis disrupts multiple physiological pathways responsible for maintaining intravascular volume, venous return, cardiac output, and tissue perfusion.[4] The rationale for delivering a fluid bolus in septic shock is to restore circulating fluid volume and optimise cardiac output and oxygen delivery.[4,5] Surprisingly, despite the fundamental role of fluid therapy in sepsis, many aspects of its use remain controversial, such as the ideal fluid type and volume.[6] This problem has been compounded by the heterogeneity in patients and the different phases of the disease.

This review article provides a quick guide for clinicians in resource-limited settings on fluid management in sepsis. A literature search was undertaken on PubMed using these keywords: Care bundles, Fluid therapy, Fluid responsiveness, Sepsis, Septic shock. Landmark trials were identified and significant findings summarised.

Discussion

Optimal fluid volume

The Surviving Sepsis Campaign (SSC) has traditionally recommended a 30 ml/kg fluid bolus during the initial resuscitation phase of septic shock, i.e. within the first 3 hours. However, this practice, initially considered a strong recommendation with low-quality evidence, has now been downgraded to a weak recommendation in the 2021 update.[2] The 30 ml/kg approach was derived from the average fluid volumes received pre-randomisation in three popular interventional sepsis trials.[2,4] This practice, now considered a standard, has also been supported by observational and retrospective studies.[7,8] In a retrospective study by Kuttab et al., patients with severe sepsis or septic shock who did not receive a

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30ml/kg fluid bolus in the first 3 hours were at increased risk of in-hospital mortality, delayed hypotension, and increased ICU length of stay irrespective of co-morbid medical conditions.[7] Unfortunately, there has been no interventional study that compared different fluid volumes for initial resuscitation in sepsis. Hence, this debate would continue. The problem with this practice is that it ignores the fact that patients with sepsis are a heterogeneous group, and thus, there is a need to individualise care.

Following initial fluid resuscitation, patients with septic shock will require further fluid therapy during the optimisation and stabilisation phase to maintain homeostasis.[4] Both liberal and restrictive fluid regimens have been utilised in clinical practice with comparable results.[9,10] Variability exists in the definition of liberal and restrictive fluid therapy, which should be borne in mind. The concern with the liberal strategy is fluid overload and its attendant risks, such as pulmonary edema, abdominal compartment syndrome, prolonged days on the ventilator and in the ICU, etc., whereas a restrictive fluid regimen may lead to hypoperfusion, aggravating organ dysfunction.

This uncertainty is further worsened by the fact that the latest update of the SSC makes no recommendation for either restrictive or liberal fluid management in the first 24 hours of resuscitation after the initial fluid bolus in patients with sepsis and septic shock.[2] Irrespective of the strategy chosen, there should be an initial assessment and ongoing re-evaluation of the response to treatment.[2] Simple tools to monitor organ perfusion and thus guide fluid administration are the heart rate, blood pressure, capillary refill time, urine output, mental status changes, serum lactate levels, etc.[4]

Optimal fluid choice

Aside from the optimal fluid volume, the optimal fluid type in sepsis remains controversial. The use of 0.9% sodium chloride is commonplace but is associated with hyperchloremic metabolic acidosis, renal vasoconstriction, increased cytokine secretion and acute kidney injury.[2,4,11,12] Balanced solutions with lower chloride concentrations and a composition closer to blood plasma were believed to offer some outcome benefits.[11] This assumption has, however, not been consistently demonstrated in clinical trials.

The single-centre SMART trial in 2018 compared balanced crystalloids (Plasmalyte and Ringer's lactate) with saline for intravenous fluid administration among critically ill adults.[12] It reported a favourable effect on the composite outcome of new death, renal replacement therapy or persistent renal dysfunction. The difference in outcomes between the two groups was greater in patients with sepsis, in which 30-day in-hospital mortality was 25.2% with balanced crystalloids and 29.4% with saline (adjusted odds ratio, 0.80; 95% CI, 0.67-0.97; P=0.02).[12] While the SMART trial demonstrated a mortality benefit with balanced crystalloids, this finding was not replicated in other clinical trials.

The BASICS trial by Zampieri et al.,[11] in Brazil, recruited over 10,000 subjects. They compared the use of a balanced solution (Plasmalyte 148) and 0.9% saline, and reported no difference in 90-day mortality. Although the study recruited different groups of patients, the outcomes (both primary and secondary) were similar in the subgroup of patients with sepsis. A limitation of these studies is that they recruited a range of critically ill patients, and thus may not be entirely applicable to sepsis. The ongoing FISSH trial in Canada, which focuses on patients with septic shock, may give further insights into this debate.[13]

Theoretically, colloids may be a better fluid for resuscitation than crystalloids as they are more likely to maintain oncotic pressure.[2,14] The literature has failed to report any clear benefit from its routine use. Annane et al., in a randomised trial, compared colloids and crystalloids for fluid resuscitation in critically ill patients with shock and reported no difference in 28-day mortality, even in the subgroup of patients with septic shock.[14] Several other studies (randomised controlled trials (RCTs) and systematic reviews) have also not found a difference in outcome between using crystalloids or colloids.[2]

Based on this and the relatively higher cost of colloids, the SSC guideline recommended using crystalloids as first-line fluid for resuscitation in sepsis. This finding is particularly reassuring for practitioners in LMICs, where colloids are not readily available. Albumin may be considered in those who have received significant volumes of crystalloids. Starches and gelatins are associated with a higher risk of renal impairment, anaphylaxis and altered haemostasis and their use in sepsis is not advised.[2] Although optimal fluid management in patients with sepsis remains uncertain, clinicians should consider the risks and benefits of fluid administration in each phase of critical illness.[4]

Prediction of fluid responsiveness

As predicted by Frank-Starling's principle, volume

expansion does not always increase cardiac output.[4,5] In about 50% of patients with septic shock (fluid non-responsive), sepsis-related myocardial dysfunction alters the relationship between preload and cardiac output.[4,5] Fluid responsiveness is defined as an increase in stroke volume of 15% in response to a fluid bolus.[5] Fluid resuscitation in non-responders results in haemodilution, increased cardiac filling pressures and fluid overload, exacerbating organ failure and shock, hence, the need to predict response to fluid bolus before its administration.[4,5,15]

Various methods of predicting fluid responsiveness have been described. The decision of which technique to use depends on the patient's condition and available monitors. These tools are commonly classified as invasive or non-invasive and static or dynamic measures. Table I highlights some of these tools and their limitations. The majority are based on the lung-heart interaction, i.e., the changes in preload during the different phases of the respiratory cycle.[4] The limitations and factors confounding the use of these methods should always be considered to avoid misinterpretation. The decision for fluid administration should not be based solely on preload responsiveness but also on the haemodynamic status (presence of peripheral hypoperfusion) and the absence of high risk for fluid overload. In addition to guiding fluid administration, fluid responsiveness can also be used to decide when to stop fluid administration.[15]

Prediction of fluid responsiveness is not commonplace in many resource-poor nations. This might be due to the unavailability of appropriate monitors and a lack of skill in undertaking these tests. In the few instances where it is used (high-risk surgery), the central venous pressure, a static and unreliable tool, is still used.[16] The passive leg-raising test is a simple, non-invasive tool for assessing fluid responsiveness. The SSC and other professional associations have recommended its use.[15] Despite its simplicity, its routine use in resource-poor facilities has been precluded by the need for direct cardiac output monitoring.

Akanbi et al., at the Ladoke Akintola University Teaching Hospital, Ogbomoso, Nigeria, in a prospective study of 25 patients with recalcitrant shock, used blood pressure and heart rate to assess fluid responsiveness following a passive leg raising test. Using this simple and readily available clinical parameter, they reported a sensitivity and specificity of about 81% and 78%, respectively.[17] This study recruited only a few patients and assessed fluid responsiveness based on changes in blood pressure and heart rate, which is not ideal. Its findings should not be disregarded, as it may be the only practicable option in resource-poor settings. It is imperative that more extensive trials comparing this method with others that directly measure cardiac output changes be undertaken to validate its usefulness.

Current Role of Care Bundles in Sepsis

Care bundles refer to a group of interventions related to a disease process that, when executed together, result in better outcomes than when implemented individually.[18] This bundle's elements are evidence-based best practices. The primary objectives of the bundle's approach to sepsis management are (I) to reduce mortality and improve patients' outcomes, (II) to ensure a more consistent and timely application of evidence-based care, and (III) to ensure reductions in clinical practice variability.[18] Bundles aim to convert complex guidelines into meaningful change in behaviour and clinical outcomes. In addition to enhancing treatment, care bundles are vital in promoting early recognition and diagnosis of sepsis.[18,19]

Table I: Measures of fluid responsiveness

Measures	Limitations
Static	
Central venous pressure (CVP)	A good marker of preload but not fluid responsiveness
Pulmonary artery occlusion pressure	Same as above
Dynamic	
Pulse pressure variation (PPV)	Unreliable in these instances: Spontaneously breathing Cardiac arrhythmias Acute respiratory distress syndrome Raised intra-abdominal pressure Right ventricular dysfunction Very high respiratory rate Low tidal volume/low lung compliance
Stroke volume variation (SVV)	Same as in PPV above
End-expiratory occlusion test	Unreliable in these instances: Spontaneously breathing Patients intolerant of a 15-s respiratory hold
Passive leg raise test	Unreliable with raised intra-abdominal pressure
Mini fluid challenge	Not well validated Repeated fluid boluses could lead to inadvertent fluid overload
Variations in diameter of the SVC and IVC	Unreliable in these instances: Spontaneously breathing Acute respiratory distress syndrome. Low tidal volume/low lung compliance. Less well studied compared to SVV and PPV. Requires some expertise
Variations in aortic blood flow velocity.	Requires some expertise

CVP- Central Venous Pressure, PPV- Pulse pressure variation, SVV- Stroke volume variation,
SVC- Superior vena cava, IVC- Inferior vena cava.

The benefit of protocolised care in sepsis was first reported in a single-centre study by Rivers et al., who described an early goal-directed therapy (EGDT) in 2001. These authors reported a 16% reduction in absolute mortality in the EGDT group compared to the control group, whose management was not based on any pre-specified protocol.[20] Several arguments have surrounded this study by Rivers et al. They bother around its external validity, considering it was a single-centre trial which recruited only 263 patients, the established inaccuracy of CVP for haemodynamic monitoring, the potential conflict of interest of the principal investigator and the evidence base for the individual elements of the protocol. Though this survival benefit has not been demonstrated in several similar studies, the role of treatment guidelines/protocols remains undisputable, considering that death from sepsis has declined tremendously over the years.[21]

The SSC has incorporated elements of this EGDT into its Bundle of care but has had to modify it over the years owing to concerns raised by three recent trials, i.e. ARISE, PROCESS and PROMISE, which were larger, international, multi-centre trials.[2,18,21–24] The latest is the Hour-1 bundle, in which interventions should begin within one hour of recognition of sepsis (Table II). It is based on the rationale that sepsis is a medical emergency, and prompt recognition and treatment are essential.[2,4] Compliance with these resuscitation bundles has been associated with a reduction in mortality rate (relative risk reduction of 25%).[18]

Unfortunately, the increasing understanding of sepsis pathophysiology and advances in care seem not to have had any measurable effect in Lower-Middle-income countries (LMICs) like Nigeria, as mortality in patients with sepsis has remained high in these parts of the world.[19] A recent study by Akase et al.[25] at a tertiary hospital in Nigeria revealed poor compliance with SSC recommendations (none of the included patients had serum lactate measurement while only 2.52% had blood culture samples taken). Challenges in implementing the sepsis bundle in LMICs include non-existent/poorly organised emergency medical services, limited diagnostic laboratory testing, varying patterns of infectious diseases, scarce resources, and poor compliance with established treatment guidelines. Thus, there is an urgent need to develop practicable care bundles in these settings.[19]

Table II: The Hour-1 sepsis bundle

Elements
1. Measure lactate level
2. Obtain blood cultures before administering antibiotics.
3. Administer broad-spectrum antibiotics.
4. Begin rapid administration of 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/l
5. Apply vasopressors if hypotensive during or after fluid resuscitation to maintain a mean arterial pressure of ≥ 65 mmHg.
6. Re-measure lactate if the initial lactate is elevated (> 2 mmol/l)

Conclusion

Despite advances in care, morbidity and mortality from sepsis remain high, particularly in LMICs.

Recommendations include:

1. Local research in LMICs is needed to identify the sepsis burden and test several elements of sepsis care.
2. To design local/institutional care bundles in resource-poor settings.
3. Encouraging education and monitoring compliance with treatment protocols.
4. More studies are needed to clarify areas of debate, such as the volume of fluid to give and the restrictive vs. liberal fluid regimen.
5. 'Protocolised' sepsis care should be promoted, albeit with local/institutional modifications and specific end goals.

Declaration section

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