Review Article

Controversies in Sepsis Management—What is the Way Forward?

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Abstract

Sepsis is life-threatening and might potentially progress from dysregulation to severe organ dysfunction. It is recognised by the World Health Organisation as a global health priority. The mortality rate for sepsis has decreased in many countries, and this is credited to the earlier recognition and treatment of this complex syndrome. In 2002, the Surviving Sepsis Campaign was launched, and there have been several revisions to the sepsis recommendations therefrom. The latest sepsis guidelines focus on viral as well as bacterial infections, and advise that initiating resuscitation and management should take place within one hour from when sepsis is initially suspected. Numerous studies and guidelines pertaining to sepsis management have been published over the past 2 decades. The use of novel therapies and alternative adjunctive therapies has tremendous potential in sepsis management. Debates amongst intensivists exist with the creation of updated sepsis guidelines and advances in treatment. The present review article provides both a summary and recommendations based on the latest clinical evidence and controversies around sepsis management.

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Introduction

Sepsis is a common and life-threatening medical condition which has high incidence and mortality rates. Health care professionals are increasingly familiar with this syndrome, and the public is increasingly conscious of its burden to society.[1] A population survey conducted in Singapore in 2010 showed that 53 out of 1067 respondents (5%) had heard of the term 'sepsis', compared with 963 out of 1067 respondents (90.3%) who were aware of 'stroke'.[2]

The definition of the entire sepsis spectrum has evolved and been refined through the past 2 decades via the efforts of passionate international experts. The definition of sepsis, as well as the diagnosis and its myriad complications, are very challenging. One would be familiar with the Surviving Sepsis Campaign (SSC), which was formed by the Society of Critical Care Medicine (SCCM), European Society of Intensive Care Medicine (ESICM), and the International Sepsis Forum, and launched at the ESICM annual meeting in Barcelona in 2002.[3] Since then, the SSC has published various iterations and revisions of the "Management of severe sepsis and septic shock"[4–7] guidelines and a recent bundle update in 2018.[8] A thorough review of sepsis and septic shock is beyond the scope of this article.

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The aim of this review is to bring to the fore some of the controversies surrounding sepsis management and how the opposing viewpoints could be balanced in daily clinical practice in Asia.

Sepsis Bundles Introduction and Evolution

In 2002, the ESICM, the International Sepsis Forum (ISF), and the SCCM launched the SSC with the Barcelona Declaration at the annual meeting of the ESICM in Barcelona.[3] The ESICM, SCCM and ISF leaders committed to reduce mortality for sepsis, and published the first SSC guidelines for sepsis management in 2004.[4] The Institute of Healthcare Improvement (IHI) created the initial "sepsis bundles".[3] The IHI suggested that promoting existing practice may not be as valuable as selecting key interventions which have evidence of reducing mortality and yet are not regularly adopted. The first SSC bundles, published in 2005, were the 6-hour (resuscitation) and 24-hour (management) bundles (Table 1).

The adherence to these bundles generated a change, with a linear correlation between reduction and adherence. Those with higher compliance to the bundles led to higher reduction in mortality.[9] In 2016, a revision of these bundles was performed and the newly published evidence transformed them into the 3-hour and 6-hour bundles (Table 1).[7] In 2018, the SSC bundles were collapsed into a single Hour-1 bundle with the explicit intention of initiating resuscitation and management immediately (Table 2).[8] The 2018 bundles were a reflection of the new sepsis definition, which was targeted at early recognition of sepsis (qSOFA).[10] The latest bundle is aimed at improving outcomes in patients with sepsis and septic shock in and outside the Intensive Care Unit (ICU).

Therefore, the recommended "Hour-1" bundle (Table 2) was implemented in emergency departments, general hospital wards as well as the ICU. This was an innovative concept but unfortunately, consensus remained sparse. The reasons for the furore can be broadly summarised into concerns of the weak evidence base being used to form the guidelines.[11] The pro/con debate by Marik and colleagues[11] clearly evaluated the controversies with the latest Hour-1 bundle. The use of the bundle may promote impetuous decisions such as liberal fluid resuscitation and excessive antibiotic usage. The risk of over-testing and over-treating patients who may not have sepsis or septic shock becomes high. Trying to incentivise care within 1 hour would pose challenges to many emergency departments, and may even cause more harm. The incorporation of these SSC guidelines and bundles into performance indicators by national regulatory bodies is also further cause for concern, which may result in physicians being pressured into administering inappropriate treatments despite their best medical judgments.

This concept has fired a passionate debate in both formal publications[11] and informal social media and online platforms. These concerns are not without merit and, as a result, the SCCM and the American College of Emergency Physicians (ACEP) have issued a joint statement recommending that hospitals not implement the Hour-1 bundle in its present form in the United States.[12]

Table 1: Surviving Sepsis Campaign Bundles[4-8]

SSC 2005	6-hour bundles	24-hour bundles
SSC 2016	3-hour bundles	6-hour bundles
SSC 2018	1-hour bundle	

Table 2: Surviving Sepsis Hour-1 Bundle[8]

Surviving Sepsis Hour-1 Bundle (2018)
Measure lactate level. Remeasure if initial lactate elevated (>2mmol/L)
Obtain blood cultures before administering antibiotics
Administer broad spectrum antibiotics
Begin to rapidly administer 30ml/kg crystalloids for hypotension or lactate >/= 4mmol/L
Apply vasopressors if hypotensive during or after fluid resuscitation to maintain a mean arterial pressure >/= 65 mm Hg

In Singapore, Emergency Medicine and Intensive Care physicians are not bound by insurance or reimbursement limitations, and they maintain the capability of providing appropriate investigations and treatments. The latest SSC guidelines have recently been assessed by the international sepsis alliance, which is composed by a group of experts. These experts have explored therapies and strategies that could be given to patients in countries outside of the United States of America (USA), Europe, Australia and New Zealand (ANZICS).

Sepsis Bundles Review: Current Practices in Sepsis Management and Novel Therapies in Sepsis Management

Lactate

Should be measured in every patient as soon as sepsis is recognised or suspected. Physicians must be mindful of the various reasons why lactate might be raised because it is a powerful predictor of the severity of sepsis. There are multiple confounders leading to an abnormal lactate value. The problem lies with its production and clearance.[13] Therefore, repeating lactate levels may aid in prognostication and correlate with clinical outcomes.

Fluid Resuscitation: Crystalloids

The rapid administration of 30ml/kg crystalloids for hypotension or when lactate exceeds 4mmol/L is not without potential harm. Clinical judgement along with tools such as point-of-care ultrasound need to be exercised, particularly in patients with reduced cardiac function or in circulatory overload.[14] Rivers and colleagues published the landmark paper in 2001, introducing the concept of early goal directed therapy (EGDT).[15] However, subsequent large multicentre randomised controlled trials (RCTs) were published and found no significant benefit between usual patient care and "protocolised EGDT"-based care. Two international RCTs could not prove reduction in mortality and improved outcomes comparable to Rivers' original paper.[16,17] EGDT has changed the concept of resuscitation and has prompted earlier sepsis recognition, initiation of antibiotics and vasopressors. New trials performed over a decade later might not show the impact of one single intervention, such as the EGDT, in the context of improved global sepsis management, when compared to the year 2000. Whilst protocolised care can change clinical behaviour, further evidence-based sepsis guidelines are required in order to make an informed decision. Invasive and non-invasive monitoring devices such as ultrasonography may be integrated in future guidance on fluid resuscitation because these are increasingly used at the bedside.

Normal saline has traditionally been the standard choice of fluids for resuscitation. Unfortunately, the use of normal saline can result in non-anion-gap metabolic acidosis, hyperchloraemia, renal vasoconstriction and increased mortality.[18] A recent trial compared balanced crystalloids and normal saline in critically ill patients. Balanced crystalloids were associated with lower mortality, renal replacement therapy and renal dysfunction.[19]

Fluid Resuscitation: Albumin

One could consider the use of intravenous infusions of albumin as an alternative to crystalloid solutions for patients at risk of volume overload (such as those with congestive cardiac failure, end stage renal failure, liver failure). Interestingly, the use of albumin was associated with a shorter duration of vasopressor use and resolution of hepatorenal syndrome in patients with cirrhosis and peritonitis.[20,21] The use of albumin has made no difference in all-cause mortality and rates of renal dysfunction leading to renal replacement therapy. It is important to note that the use of albumin in patients with traumatic brain injury had worse outcomes compared to saline-treated patients.[22] A recent meta-analysis by Martin et al suggests that the use of albumin may help restore hemodynamic endpoints in a more effective approach.[23] Guidelines do not include a clear recommendation to guide physicians what constitutes a substantial amount of crystalloids, and the timing when albumin should be administered. Exactly when physicians should switch to albumin remains an important unanswered question.

The differences in outcomes between using crystalloids and albumin are not significant, but the use of albumin will be restricted due to its availability and cost. Hence, the current evidence suggests the use of balanced crystalloids as the gold standard in patients with sepsis. More importantly, multiple studies have linked aggressive fluid resuscitation to be an independent variable to mortality in patients with sepsis, suggesting that the optimisation phase in sepsis is paramount in fluid management, and continual assessment of fluid status and responsiveness is vital.[24,25]

Fluid Resuscitation: Colloids

There is conflicting evidence regarding the use of colloids in sepsis. The use of colloids and crystalloids was compared in the CRISTAL trial, and there was no mortality benefit between the groups.[26] Risks outweigh benefits for most colloids including dextran, gelatin and hydroxethyl starch, as these are contraindicated in the presence of renal insufficiency.

Vasopressors

Noradrenaline remains the first line vasopressor in most non-cardiac ICUs. The 2012 SSC guidelines recommended early initiation of noradrenaline in patients with low diastolic blood pressure. However, the 2016 SSC guidelines were unclear with the timeliness to initiation of noradrenaline.[7] The Hour-1 bundle (Table 2) clearly recommended the use of vasopressors, if patients are hypotensive during or after fluid resuscitation, to maintain mean arterial pressure of over 65 mm Hg.[8]

Arguably, the intent of the guidelines in recommending early fluid resuscitation does, in theory, play an important role, as it prevents hypoperfusion to vital organs.[27] This is essential if there is inadequate intravascular volume. The early initiation of vasopressors without adequate fluid resuscitation may deprive blood flow to vital organs.

However, previous retrospective studies had shown that early initiation of noradrenaline was associated with earlier reversal of hemodynamic abnormalities, lower incidences of arrhythmias and cardiogenic pulmonary oedema.[28] Moreover, early, compared to delayed, initiation of vasopressors has been associated with improved survival.[29] In refractory hypotension, the use of vasopressin is indicated as an adjunct with noradrenaline, and to decrease noradrenaline dosage. Vasopressin has not been shown to have a difference in mortality or improve the number of kidney failure-free days.[30,31] An ongoing multicentre RCT is currently ongoing comparing liberal and restrictive fluid strategies with early vasopressor resuscitative strategies.[32]

The use of angiotensin-II has limited safety and efficacy data. The ATHOS-3 trial was underpowered to detect rare adverse events and differences in clinical outcomes including mortality. Moreover, the incidence of arterial and venous thrombosis related to the use of angiotensin-II and the trial's short term follow up limit conclusions regarding the long-term safety and efficacy of angiotensin-II.[33]

The early use of vasopressors remains controversial, having only low-level evidence available. The technicalities of having to administer higher doses of vasopressors through a central venous line may limit its use, but a recent systemic review suggested low dose noradrenaline, dopamine, phenylephrine can safely be given peripherally.[34] The current evidence recommends a haemodynamically-guided conservative fluid resuscitation strategy with early recognition of vasopressor initiation.

Stress Ulcer Prophylaxis

The SSC guidelines recommend stress ulcer prophylaxis in patients with sepsis, who have risk factors of gastrointestinal bleeding. The strongest clinical predictors of gastrointestinal bleeding include mechanical ventilation beyond 48 hours and coagulopathy.[7] However, stress ulcer prophylaxis may be associated with increased risks of infections such as hospital-acquired pneumonia and clostridium-difficile infection. With similar rates of gastrointestinal bleeding in patients without prophylaxis, the use of stress ulcer prophylaxis may not be required and may even be harmful and should be reserved for patients with risk factors. Patients should be periodically evaluated for the continued need for prophylaxis.[35,36]

Corticosteroids (Glucocorticoids)

The concept of relative adrenal insufficiency in sepsis was previously supported by Annane and colleagues.[37] The CORTICUS trial initially concluded that there was no mortality benefit, but faster resolution of shock.[38] This evidence was further supported by the latest 2 trials: ADRENAL and APROCCHSS,[39,40] with both collectively publishing data supporting the use of hydrocortisone and hydrocortisone/fludrocortisone, respectively, in septic shock. However, the timing for starting the use of steroids differed between these trials (CORTICUS – within 12 hours, ADRENAL and APROCCHSS – within 4–6 hours). Mortality benefit was noted in only 1 study (43% vs 49%).[40] Corticosteroids may be more beneficial in patients who are sicker, and should not be administered prophylactically.[41] The PROGRESS registry demonstrated that steroid use in severe sepsis was widespread even in patients not requiring vasopressors.[42]

These studies have allowed further investigations into the use of combination therapy including hydrocortisone, ascorbic acid and thiamine for septic shock (see section on combination of hydrocortisone, ascorbic acid, thiamine.)

Novel Therapies in Sepsis Management

Despite decades of research, the cornerstone of sepsis management has remained disappointingly unchanged. Several novel therapeutic approaches have arisen and are listed below. However, most remain controversial, without a body of strong evidence.

Extracorporeal Techniques

Extracorporeal immunomodulation has been studied quite extensively. The postulated mechanisms of action

include (1) reducing cytokine concentration, so as to reduce the overall inflammatory effects as well as to allow leukocyte chemotaxis to the infected areas with higher cytokine concentration, (2) removing pathogen-associated molecular patterns (PAMPS) and minimising the inflammatory triggers.[43]

Adsorption with the polymyxin B-fibre column (PMX-HP) is currently the best-studied option for endotoxin removal. The original EUPHAS trial suggested haemodynamic benefits and mortality reduction as a secondary outcome in patients with intra-abdominal gram-negative infections,[44] but other studies differed. The EUPHRATES (Evaluating the Use of Polymyxin B Haemoperfusion in a Randomised Controlled trial of Adults Treated for Endotoxaemia and Septic Shock) trial was thus conducted, but no mortality benefit was demonstrated among patients with septic shock and increased endotoxin activity levels (≥ 0.6).[45] Interestingly, this could be due to the PMX-HP cartridge limitations[46] and those with endotoxin levels of 0.6–0.89 actually did have mortality benefit, haemodynamic benefits and increased ventilator-free days. The relative timing, dose, and duration of polymyxin B haemoperfusion may have been insufficient to significantly reduce the endotoxic burden, which is supported by failure of significant reductions in endotoxin activity assay levels. This warrants further evaluation.

Another proposal is to remove pro-inflammatory middle molecular-weight molecules via high-volume haemofiltration with high ultrafiltration rate (>50 ml/kg per hour).[43] However, trials demonstrating benefit have remained elusive. The largest trial (IVIORE: High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury) failed to demonstrate any difference in mortality when compared to the standard volume group (70 vs 35 ml/kg per hour) among patients with septic shock and acute kidney injury (AKI). The evidence suggests against routinely incorporating extracorporeal techniques in patients with septic shock.

Alternative Adjunctive Therapies

Administration of granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) aims to promote neutrophil proliferation, differentiation and enhance their anti-bacterial properties. It was shown that among patients with neutropenic sepsis, enhancing neutrophil recovery and reducing the neutropenia duration allowed earlier reversal of shock.[47] However, the indication in neutropenic sepsis unrelated to chemotherapy and non-neutropenic sepsis is less clear-cut. Clinical trials are few and of inconsistent quality, and further research is warranted.

Septic patients have low plasma immunoglobulin (IgG) concentrations, but the immunocompromised state in sepsis is in fact more complex.[48] Intravenous human normal immunoglobulin (IVIG) therapy was intended to replenish the immunoglobulin levels, to scavenge and remove the inflammasomes and signalosomes.[49]

Different meta-analyses have sent conflicting signals on IVIG efficacy, owing to the heterogenous populations studied and the small sample sizes. However, the largest IVIG study (SBITS study) did not demonstrate any mortality benefit, and showed that patients with highest IgG concentrations had a significantly higher mortality in a risk-adjusted calculation compared to reference quartile. [50,51] This has led to the negative recommendation in the latest surviving sepsis guidelines.[7] However, some patient subsets may still benefit, such as those with streptococcal toxic shock syndrome, where there is mortality benefit.[52]

Similar to IVIG and haematopoietic growth factors, therapeutic plasma exchange (TPE) aims to maintain important plasma proteins and remove the pro-inflammatory mediators. However, studies are few and small, although meta-analysis does suggest a potential mortality benefit.[53] TPE appears to be safe and demonstrates haemodynamic benefits.[54] However, this remains in the experimental realm and requires further evaluation.

Immune checkpoint inhibition (ICI) has revolutionised cancer treatment through inhibiting the actions of programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1). In septic patients, studies have shown that the sepsis-induced immunosuppressed state was perpetuated by the up-regulation of PD-1/PD-L1.[55] As such, ICI is now part of the new frontier of sepsis management. Several phase 1 trials have shown that ICI is well-tolerated.[56] Larger-scale studies are ongoing.

Vitamin D has effects on skeletal and non-skeletal muscles, blood vessels, cell proliferation and differentiation. Vitamin D deficiency may potentially lead to worsening organ dysfunction. A large RCT is currently looking at the use of high dose Vitamin D in critically ill patients with Vitamin D deficiency.[57]

Combination of Hydrocortisone, Ascorbic Acid, Thiamine (HAT)

Marik and colleagues recently demonstrated a before-after study to demonstrate a significant mortality benefit

Table 3. Summary of Sepsis Management

Intervention	Recommendations for Asia
Measurement of lactate	This is used for guidance for fluid resuscitation but it is not a therapy. It may be correlated with mortality.[13]
Fluid Resuscitation: Crystalloids	Balanced crystalloids for sepsis or septic shock.[14–17,19]
Fluid Resuscitation: Albumin	Second line for fluid resuscitation when patients require a substantial amount of crystalloids.[20–23]
Fluid Resuscitation: Colloids	No evidence based on current literature.[26]
Vasopressors	Use of vasopressors if inadequate response to fluid resuscitation in septic shock.[28–31]
Steroids	Weak recommendation.[38–41]
Stress Ulcer Prophylaxis	Limited evidence.[35,36]
Novel therapies in sepsis management	
Extracorporeal Techniques	Not to be routinely incorporated based on current literature.[43–46]
Granulocyte-Colony Stimulating Factor	Indicated in neutropenic sepsis.[47]
Intravenous human normal immunoglobulin (IVIG)	Recommended in streptococcal toxic shock syndrome.[49,50,52]
Therapeutic Plasma Exchange	More evidence required.[53,54]
Immune Checkpoint Inhibition	More evidence required.[55,56]
Vitamin D Therapy	More evidence required.[57]
Hydrocortisone/ascorbic acid/thiamine	More evidence required.[58–60]

in patients receiving HAT (40.4% in the control group versus 8.5% in the treatment group) with minimal side effects.[58] Emerging clinical data have suggested that this combination is likely to work owing to the synergistic effects of the individual components. In septic patients, thiamine deficiency is common. Without thiamine, pyruvate cannot convert to acetyl coenzyme A, thus impairing aerobic respiration and generating lactate instead. Thiamine deficiency also leads to a reduction in NADPH generation via hindering the pentose phosphate pathway. On the other hand, vitamin C serves other important functions, ranging from its antioxidant effects and its unique importance in the generation of endogenous vasopressors. The role of steroids in sepsis management has been elaborated earlier.[38–41] Vitamin C also restores impaired steroid receptor function while steroid separately upregulates the sodium-vitamin C transporter. When combined, their effects exponentially increase.

The recent VITAMINS trial[59] revealed that there were no significant differences in their primary endpoints (vasopressor use/mortality), but the intervention group did have a significant change in SOFA score in septic patients. The mean time to administration of treatment was 12 hours, and 40% of patients had already been started on steroids prior to study enlistment. Despite the theoretical benefits of early HAT therapy (given <6H), early therapy only showed significance in patients with hypoalbuminaemia and higher SOFA scores.[60] This could be masked by various confounders and we await further high-quality studies to assess the clinical significance of HAT. In fulminant septic shock, it may be too late to observe an effect from HAT, although this is occasionally practised.

A summary of the interventions for sepsis/septic shock based on current literature along with the authors' recommendations for Asia are listed in Table 3.

Conclusion

The management of sepsis has transformed over the past 2 decades. The use of different management options is deferred to the intensivists. Recognition and early treatment of this condition have been paramount for improving outcomes. Public awareness has raised concerns and increased donations and money invested in research and technology for the treatment of sepsis. The question lies as to whether or not bundles are required when our management of sepsis has improved remarkably over the years. Notwithstanding novel therapies and adjunctive therapies, further studies are

required to look at achieving earlier source control and conservative versus liberal oxygen therapy–and the importance of these parameters in helping to enhance our management of sepsis.

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