

A current appraisal of evidence for the approach to sepsis and septic shock

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Abstract: Sepsis is a life-threatening syndrome of a dysregulated host response to infection. Despite advances in diagnosis and treatment, sepsis remains a significant cause of morbidity and mortality. Many aspects of the diagnosis and clinical management of sepsis require further study and remain controversial. This review aims to summarize relevant literature and controversies regarding the evaluation and management of sepsis and septic shock.

Keywords: critical care, intensive care, sepsis, septic shock, shock

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Introduction

Sepsis is a life-threatening syndrome of a dysregulated host response to infection.¹ Despite advances in diagnosis and treatment, sepsis remains a significant cause of morbidity and mortality. Many aspects of the diagnosis and clinical management of sepsis require further study and remain controversial. This review aims to summarize relevant literature and controversies regarding the overall evaluation and management of sepsis and septic shock.

Evolving definitions

Although sepsis has been the focus of clinical and biologic inquiry for many decades, attempts to develop a clear and consistent definition of the syndrome have proven challenging and remains a subject that is under ongoing review and evaluation.² Sepsis was defined in a 1991 consensus statement as the systemic inflammatory response syndrome (SIRS) in reaction to infection (Table 1). Sepsis complicated by organ dysfunction was defined as severe sepsis, and septic shock was defined as hypotension due to sepsis despite adequate fluid resuscitation (Table 2).³ The goals of these definitions were to facilitate identification of patients with sepsis early in their course, and to create guidelines for recruitment of patients into clinical trials with more uniform clinical criteria. This 1991 definition was reviewed in 2001, in a

subsequent consensus statement.⁴ While the authors acknowledged limitations in using SIRS as a definition of sepsis, particularly the lack of clinical specificity, they nevertheless agreed that SIRS was a useful clinical concept, and no major changes were made to the definitions established in 1991. Efforts were made to conceptualize ways to include biologic markers into the sepsis criteria (e.g. levels of circulating pro-inflammatory cytokines),² although to date there has not been agreement as to how to do this.

Subsequent studies raised further questions regarding the utility of SIRS as a useful screening tool for sepsis. Churpek and colleagues published a retrospective review of 269,951 ward patients, and found that 47% met two of four SIRS criteria at some point during their admission, suggesting that SIRS might be an overly sensitive screening tool.⁵ Conversely, a retrospective analysis of 109,663 patients in Australia and New Zealand with infection and organ failure found that 87.9% had SIRS-positive sepsis, while the remainder had SIRS-negative sepsis, with similar outcomes to the SIRS-positive sepsis group.⁶ Thus, use of two or more SIRS criteria to define sepsis in this cohort missed approximately 12% of patients with infections accompanied by substantial organ failure and mortality. The authors of this study also found mortality increased linearly with each additional category of SIRS criteria met (up to a

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Table 1. Systemic inflammatory response syndrome (SIRS) criteria. In Sepsis-1 and Sepsis-2, sepsis was defined as the presence at least two of the above criteria due to infection. As of Sepsis-3, SIRS criteria are no longer used in the definition of sepsis.

SIRS criteria	
Temperature	> 38°C or < 36°C
Heart Rate	>90 beats per min
Tachypnea	Respiratory rate >20 breaths per min or a PaCO ₂ of <32 mmHg
White blood cell count	>12,000/ μ L ³ or <4,000/ μ L ³ , or >10% immature (band) forms

Table 2. Changes in definitions of sepsis and sepsis related syndromes after Sepsis-3 consensus statement.

Era	Syndrome	Definition
Prior to Sepsis-3	Sepsis	SIRS in response to infection
	Severe Sepsis	SIRS in response to infection, with organ dysfunction
	Septic shock	Hypotension due to sepsis (defined by SIRS criteria) despite fluid resuscitation
After Sepsis-3	Sepsis	SOFA increase \geq 2 in response to infection
	Severe Sepsis	Eliminated in Sepsis-3
	Septic shock	Sepsis (as defined by SOFA), with hypotension not responsive to fluid resuscitation, and a lactate level \geq 2 mmol/L

SIRS, Systemic inflammatory response syndrome. SOFA, Sequential organ failure assessment.

total of four), and that there was no threshold effect at two SIRS criteria. Some clinical trials have sought to improve the specificity of the SIRS criteria for identifying infection. For example, a trial of rosuvastatin for acute respiratory distress syndrome (ARDS) in patients with sepsis excluded patients who did not have fever, hypothermia, leukocytosis, leukopenia, or more than 10% band forms as part of their SIRS criteria.⁷ However, no data exist to support these revised criteria for broader use.

Sepsis-3, published in 2016, was the first major consensus revision in the definition of sepsis in 25 years, and aimed to address perceived shortcomings of the prior definitions, including the higher sensitivity but lower specificity of SIRS observed in some studies, and the redundancy of severe sepsis, which was eliminated from the definition (Table 2).¹ Sepsis was defined broadly as life-threatening organ dysfunction caused by a

dysregulated host response to infection. Organ dysfunction was assessed using the sequential organ failure assessment (SOFA) score, which assigns 0–4 points across six organ systems based on the severity of dysfunction.⁸ Sepsis-3 defined sepsis as an increase of at least 2 points in the SOFA score from baseline. The SOFA score was felt to have better predictive validity than SIRS for mortality, and its predictive validity was not significantly different than the more complex scoring logistic organ dysfunction scoring system (LODS), thus lending support for its use as a component of the definition of sepsis.⁹ Septic shock was defined as sepsis, plus hypotension not responsive to fluid resuscitation and a lactate level \geq 2 mmol/L, predicting a mortality of at least 40% (Table 2).¹

Diagnosis, screening, and severity of sepsis

Prior to release of the Sepsis-3 definition, SIRS was used both as a screening tool as well as part of

the criteria for diagnosis of sepsis. With elimination of SIRS from the Sepsis-3 consensus definition, there remains persistent discussion over how best to screen for sepsis. Due to its complexity, the SOFA was not intended, or easily used, for sepsis screening, as it relies on data that is not always available at the bedside. The quick SOFA (qSOFA) was developed as a tool to gauge severity of sepsis as part of the Sepsis-3 consensus, and aimed to identify patients, primarily outside the ICU, with suspected infection who are likely to develop complications of sepsis.¹ The qSOFA has also been proposed by some as a means of screening for sepsis, though there is not uniform agreement on this subject.¹⁰⁻¹² A positive qSOFA score is comprised of two of the following three risk factors: respiratory rate greater than 22 breaths per min, systolic blood pressure of less than 100 mmHg, and altered mental status (as measured by a Glasgow Coma Scale <15). Subsequent data regarding the utility of the qSOFA score in predicting mortality have been mixed. Raith and colleagues investigated the predictive validity of SOFA *versus* qSOFA *versus* SIRS for in-hospital mortality in a large retrospective cohort of ICU patients in Australia and New Zealand, and found the SOFA score to be superior to both qSOFA and SIRS for predicting in-hospital mortality, though, notably, the qSOFA was not initially developed for use in the ICU.¹² One study set in 30 participating emergency departments across four countries in Europe showed superior performance of qSOFA when compared with SIRS or severe sepsis in predicting in-hospital mortality.¹¹

Validation studies are ongoing in an effort to determine the utility of qSOFA and other sepsis diagnosis, screening, and prediction tools. The qSOFA has also been examined in more resource limited settings. In a retrospective secondary analysis of nine prior studies, including diverse cohorts of hospitalized patients in low- and middle-income countries, a high qSOFA score (≥ 2) was associated with an increased risk of death overall [19% for a high qSOFA score *versus* 6% for a low (0) or moderate (1) qSOFA score].¹³ More recently, Rhee and colleagues have published an analysis evaluating the performance of a new electronic SOFA (eSOFA) score against the SOFA score.¹⁴ The eSOFA score is a simplified organ score optimized for electronic medical record use, and was created by the United States Centers for Disease Control and Prevention to

facilitate retrospective surveillance of sepsis events. The authors analyzed 942,360 patients from 111 US hospitals retrospectively, and found that the eSOFA score identified a smaller, but sicker, group of patients when compared with the SOFA score. Furthermore, the eSOFA had the advantage of being easier to calculate, and might be feasible for more widespread electronic health sepsis surveillance.

Of note, it has been reported that the qSOFA performs worse than several other scoring systems such as Modified Early Warning Score, and the National Early Warning Score when predicting death and ICU transfer; both these scoring systems are simple enough to be calculated at the bedside.¹⁰ Other scoring systems are more complex. The Acute Physiology and Chronic Health Evaluation (APACHE) IV score is based on multivariate logistic regression, and builds upon prior APACHE scoring symptoms.¹⁵ While APACHE IV scores are typically too complex to be calculated at the bedside, they have utility in assessing illness severity in a research setting. The SOFA score performs only slightly worse than APACHE for predicting ICU mortality, while having the advantage of requiring less data collection.¹⁶

Thus, in aggregate, there remains ongoing discussion and investigation regarding optimal definitions, screening, and predictors of outcomes in sepsis. Some early critiques of the Sepsis-3 consensus statement include the limited applicability of the definitions in resource poor settings that do not have access to the rapid laboratory testing required for early calculation of a SOFA score (although, as above, more work is ongoing in this area assessing the applicability of the qSOFA score to these settings), as well as the lack of integration of biomarkers in sepsis to help define prognosis or outcomes for subgroups of patients.¹⁷ The most recent Surviving Sepsis Campaign guidelines suggest that SIRS as a sensitive screening tool for sepsis may still be justified, so as not to miss cases of possible sepsis. Diagnosis of sepsis with the SOFA score to evaluate organ dysfunction in the setting of infection and use of qSOFA to predict severity and outcome of sepsis as recommended by the Sepsis-3 consensus document has been recommended. As with prior recommendations, refractory hypotension and an elevated lactate in the setting of sepsis should point towards septic shock.¹⁸

Antibiotics and source control

Timely administration of antibiotics is an important determinant of survival in sepsis and septic shock. Antibiotic selection should be based on the host and suspected site of infection, though sufficiently broad in terms of coverage, as inappropriate antibiotic selection has been associated with increased mortality.¹⁸ Delays of greater than 1 h between initial triage for sepsis and administration of antibiotics have been associated with increased mortality.¹⁹ New York State began requiring hospitals to follow protocolized identification and treatment of sepsis in 2013.²⁰ The bundled treatment involved collection of blood cultures, administration of antibiotics, intravenous fluid administration, and lactate measurements within 3 h of triage. Review of outcomes for sepsis and septic shock in New York State following the implementation of these guidelines showed that each additional hour in delay of completion of the bundle was associated with a linear increase in mortality.²¹ The source of infection is important in the treatment of sepsis. Timely source control, when necessary to eliminate a source of infection, is critical. For example, in patients with abdominal sepsis from gastrointestinal perforation, delay in surgical source control was associated with increased 60-day mortality.²² The Surviving Sepsis Campaign guidelines recommend source control as soon as is feasible.¹⁸

Novel antimicrobial strategies

While it is acknowledged that early effective antimicrobial therapy is a keystone to the management of sepsis, the rising prevalence of multidrug resistant organisms (MDRO) makes the selection of appropriate antibiotics for sepsis increasingly challenging. Despite this trend, only limited numbers of novel antimicrobials have been licensed since 2012.²³ Thus, the development and understanding of novel antimicrobial approaches is critical to improving outcomes in sepsis. While a detailed review is beyond the scope of this paper, we will highlight a few recent strategies to identify novel antimicrobials.

One recent strategy targets resistance mechanisms, thus extending the spectrum of currently used antibiotics. For example, methicillin-resistant *Staphylococcus aureus* (MRSA) uses Ser/Thr protein kinase (STK1) for cell wall biosynthesis. While not necessary for survival, STK1 deficient

strains become susceptible to ceftriaxone and ceftaxime. Recently, Kant and colleagues described a novel small molecule, Inh2-B1, which binds STK1 and reduces MRSA resistance to cephalosporins.²⁴ The combination of a third-generation cephalosporin and Inh2-B1 allows mice to survive otherwise lethal MRSA challenge. Two antimicrobial therapies recently approved by the United States Food and Drug Administration have extended the spectrum of previously approved antibiotics by pairing them with a novel beta-lactamase or carbapenemase. Ceftazidime-avibactam was shown in a randomized phase III, pathogen-directed, open-label trial ($n=333$ patients) to be as effective as best available therapy for complicated urinary tract or intraabdominal infections with ceftazidime-resistant Enterobacteriaceae or *Pseudomonas aeruginosa*.²⁵ Meropenem-Vaborbactam was shown to be more likely to achieve a clinical cure in carbapenem-resistant Enterobacteriaceae infections, with less mortality and nephrotoxicity when compared with best available therapy in a phase III randomized, controlled, open-label trial ($n=77$ patients).²⁶

Another recent strategy combined improved understanding of mechanisms of virulence with high throughput screening for compounds that interfere with these mechanisms. *Neisseria meningitidis*, depends on interactions between its type IV pilus and human endothelial cells to cause disease. Aubey and colleagues used a high throughput screen to identify compounds with low toxicity that inhibited this virulence factor, and identified three compounds of interest.²⁷ Notably, these compounds were not bactericidal; however, they prevented adhesion to cultured human endothelial cells, and caused bacteria cultured in the presence of human endothelial cells to become detached from these cells.

Targeted antibodies may also be a viable therapeutic strategy, especially for organisms like *Acinetobacter baumannii* that have high levels of antibiotic-resistance. Nielsen and colleagues developed a monoclonal antibody against extremely drug resistant (XDR) *A. baumannii* that had a synergistic bactericidal effect with Colistin, improved macrophage uptake of the pathogen, and rescued mice from lethal infection with this organism.²⁸

Yet another strategy involves the modification of naturally occurring antimicrobial peptides

(AMPs) to enhance activity. Chen and colleagues identified three endogenous AMPs to which the addition of a C-terminal cysteine significantly enhanced activity against gram-negative bacteria.²⁹ These compounds were efficacious with no observed toxicity in mouse models of gram-negative sepsis. In separate work, Kim and colleagues modified the AMP papiliocin to increase its interaction with bacterial cell membranes, and were able to significantly improve survival of gram-negative sepsis in mice.³⁰

Early goal-directed therapy

In 2001, Rivers and colleagues published a study of early goal-directed therapy (EGDT) for the treatment of sepsis.³¹ A bundle of interventions, including placement of a central venous catheter, intravenous fluids to achieve a central venous pressure (CVP) of 8–12 mmHg, mean arterial pressure greater than or equal to 65 mmHg achieved with vasopressors if necessary, and central venous oxygen saturations of greater than or equal to 70% achieved with red cell transfusions and dobutamine, was shown to decrease in-hospital mortality from 46.5% in the control arm to 30.5% in the intervention arm.

Subsequent studies of protocolized care for sepsis have aimed to identify the aspects of the bundle in the Rivers trial that were most associated with survival benefit, with the widespread belief that earlier administration of antibiotics and fluid resuscitation in the EGDT group may have played a role in the benefit observed for the intervention group in that study. The protocolized care for early septic shock (ProCESS) trial, published in 2014 compared three arms; (1) the bundle of care described in the original Rivers trial, (2) a similar arm without the use of inotropes or blood transfusions, and (3) usual care.³² ProCESS found no difference in mortality in any arm. The Australasian resuscitation in sepsis evaluation (ARISE) study, published in 2014, compared EGDT to usual care, and found no mortality benefit.³³ The protocolized management in sepsis (ProMIse) trial, published in 2015, similarly compared EGDT to usual care and found no mortality difference.³⁴ ProCESS, ARISE, and ProMIse all found lower mortality from septic shock when compared with the control arms in the original EGDT study. One potential explanation for the lack of benefit shown in subsequent

studies of EGDT is that usual care for sepsis has changed since the publication of the Rivers study. Indeed, a retrospective analysis showed that, between 2003 and 2013, patients received increasingly early aggressive fluid resuscitation.³⁵

Subsequent trials have individually investigated other aspects of EGDT. The transfusion requirements in septic shock (TRISS) trial randomized patients to a target hemoglobin to transfusion for hemoglobin less than 7 g per deciliter *versus* 9 g per deciliter and found no significant difference in mortality.³⁶ A single center trial has also examined the necessity of central venous catheters, even in patients requiring vasopressors; this study demonstrated that vasoactive medications could be administered peripherally with relatively low risk of extravasation or morbidity.³⁷

Fluid strategy

While the value of early administration of intravenous fluids in sepsis and septic shock is uncontroversial, the amount of fluid administered and when and when to initiate vasoactive agents remain areas of active investigation. It is likely that neither under-resuscitation, nor excess fluid administration, is beneficial in sepsis. The current clinical guidelines suggest using a targeted fluid resuscitation strategy, but do not provide direction as to how this should be done specifically, and there are no current studies that provide guidance in this area.^{18,38} Possible suggested targets for fluid resuscitation include: monitoring a blood pressure/heart rate response, monitoring urine output, monitoring CVP and central venous oxygen saturation, pulse pressure variation, lactate clearance, and dynamic responses such as to fluid boluses or passive leg raising.^{18,38} The Crystalloid liberal or vasopressors early resuscitation in sepsis (CLOVERS) trial is an ongoing multicenter trial comparing a restrictive fluid strategy with preferential early use of vasopressors to treat hypotension in sepsis *versus* a liberal fluid strategy with early intravenous fluid boluses for patients upon presentation with sepsis-induced hypotension.³⁹

Fluid selection can have an impact on mortality. Hydroxyethyl starch, a colloid solution previously used for resuscitation, was associated with increased mortality when compared with normal saline.⁴⁰ The use of hydroxyethyl starch is thus contraindicated in septic shock. The albumin

Italian outcome sepsis (ALBIOS) study compared resuscitation with 20% albumin and crystalloid solution to crystalloid alone and found no significant mortality benefit.⁴¹ Nevertheless, the Surviving Sepsis Campaign guidelines support the use of albumin late in resuscitative efforts to limit the development of volume overload.¹⁸ A comparison of normal saline to balanced crystalloid (either lactated Ringer's solution or Plasma-Lyte A) for resuscitation in critically ill patients in a single-center study found a small but significant benefit to balanced crystalloid in the development of a composite endpoint of death, persistent renal dysfunction, or new renal replacement therapy.⁴² This study is in keeping with concern from some investigators regarding potential harmful renal effects of the chloride load from normal saline resuscitation. While additional studies to confirm this finding will be necessary, many practitioners have begun to favor use of balanced crystalloids over normal saline for fluid resuscitation in sepsis.

Choice of vasoactive agent

Several vasoactive agents can be used to support perfusion in septic shock, including catecholamines and vasopressin.⁴³ These agents function by stimulation of cardiac contractility and/or peripheral vasoconstriction, depending upon individual agents' mechanism of action. The Surviving Sepsis Campaign suggests norepinephrine, a potent agonist of both alpha and beta receptors, as the initial vasopressor of choice in septic shock.¹⁸ Norepinephrine is an endogenous catecholamine that stimulates alpha and beta receptors, and dopamine is an endogenous catecholamine that stimulates dopamine, alpha, and beta receptors. Norepinephrine has been compared with dopamine in a randomized controlled trial for patients with undifferentiated shock.⁴⁴ There was no difference in mortality at 28 days; however, more arrhythmias were observed in those patients receiving dopamine. Dopamine can have different physiologic effects based on the dose, with lower doses of dopamine having been shown to cause splanchnic vasodilation in healthy volunteers. However, when studied in patients with critical illness and shock at risk of renal injury, the use of low dose dopamine did not prevent renal injury.⁴⁵

Vasopressin is an endogenous, centrally released hormone with vasoactive properties that may be

depleted in patients with shock. Two large trials have investigated the use of vasopressin in addition to catecholamines. The first trial compared low dose vasopressin (0.01–0.03 units (U)/min) as an initial vasopressor added to low-dose norepinephrine *versus* norepinephrine alone at higher doses in 778 patients, and found no difference in mortality at 28 days.⁴⁶ A *post hoc* analysis of patients with less severe septic shock found that the use of vasopressin was associated with significantly reduced mortality, from 35.7% to 26.5% in this group, supporting the notion of vasopressin as an add-on 'rescue' vasopressor to norepinephrine. Another trial examined potential renal benefits of early vasopressin in patients with septic shock. This 2 × 2 randomized clinical trial assigned 409 patients to high dose vasopressin (0.06 U/min) with or without corticosteroids, or norepinephrine with or without corticosteroids. There was no difference in kidney-failure-free days between groups, though there was reduced use of renal replacement therapy in the vasopressin group, suggesting future trials will be important for further assessment.⁴⁷ Neither study found harm associated with administration of vasopressin. The Surviving Sepsis Campaign guidelines advocate for vasopressin to be used as the second vasopressor following administration of norepinephrine if a MAP target is not achieved, and many clinicians use vasopressin as a 'rescue' vasopressor once norepinephrine requirements increase.¹⁸

A second noncatecholamine agent, angiotensin II, has been studied in a limited capacity in vasodilatory shock.⁴⁸ Angiotensin II is an endogenous hormone that is a part of the renin-angiotensin-aldosterone system. A total of 344 patients with vasodilatory shock requiring vasopressors were randomized to angiotensin II or placebo as an add-on vasopressor. Those patients receiving angiotensin were more likely to reach prespecified MAP goals (increase in 10 mmHg or at least 75 mmHg) than those receiving placebo (69.9% *versus* 23.4%). There were no statistically significant differences in 28-day mortality, though the study was not powered to detect differences in mortality. Further study is needed to determine the role of angiotensin II in the management of patients with septic shock, though this study raises hope that angiotensin II might represent a novel class of vasopressor agents for refractory shock.

Steroids in sepsis

While corticosteroids have immunosuppressive effects that may be harmful in sepsis, these effects may be outweighed by beneficial anti-inflammatory and vasoactive effects, for some patients. High doses of steroids have been shown to be harmful in sepsis⁴⁹; however the role of ‘stress dose’ (i.e. low-dose hydrocortisone, 200–300 mg/day for 5–7 days) hydrocortisone in sepsis and septic shock is less clear. Several large, randomized trials have been done to determine the optimal use of low-dose corticosteroids in patients with sepsis and septic shock. Unfortunately, the findings of these trials have often been conflicting.⁵⁰ Some authors have postulated that patients with sepsis develop an acquired corticosteroid insufficiency.⁵¹ Unfortunately, efforts to define or create diagnostic criteria for critical illness-related corticosteroid insufficiency have not been fruitful.⁵² We will briefly review some of the key studies of corticosteroids in septic shock.

In 2002, Annane and colleagues randomized 300 patients in France with septic shock to either placebo or low-dose hydrocortisone and fludrocortisone.⁵³ The study also administered a corticotropin challenge to all enrolled patients to identify ‘relative’ adrenal insufficiency, that is, those patients who were not absolutely adrenally insufficient, but without a substantial response to corticotropin challenge, and were therefore postulated to lack adrenal ‘reserve’ in the setting of physiologic stress from septic shock. A total of 73% of patients were found to be nonresponders to corticotropin challenge. The entire cohort had very high overall mortality (58%), and, notably, the beneficial effects of steroids were greater in those patients who did not respond to corticotropin challenge (i.e. those with relative adrenal insufficiency), with a significant difference in mortality (63% *versus* 53% favoring the steroid arm). Patients who did respond to corticotropin challenge had no statistically significant difference in 28-day mortality with low-dose steroids (53% *versus* 61% favoring placebo).

Unfortunately, follow-up trials have not shown consistent results. CORTICUS, published in 2008, randomized 499 patients with septic shock to low-dose hydrocortisone *versus* placebo.⁵⁴ This study also assessed for relative adrenal insufficiency using a corticotropin challenge, and found that 46.7% were nonresponders. There was no

improvement in 28-day survival with corticosteroids. Even when including only those patients who did not respond to corticotropin challenge, there was no survival benefit observed. While there was faster resolution of shock in the corticosteroid arm, there was also a nonstatistically significant trend towards increased infections in the corticosteroid group.

HYPRESS, published in 2016, randomized 353 patients with severe sepsis (without shock) to low-dose hydrocortisone *versus* placebo and found no reduction in the risk of developing septic shock (primary outcome), or mortality (secondary outcome) with corticosteroids.⁵⁵ In 2018, two large trials were published investigating the role of steroids in sepsis. ADRENAL included 3800 patients with septic shock and mechanical ventilation randomized to hydrocortisone or placebo, and found no significant difference in 90-day mortality (primary outcome, 27.9% mortality in the hydrocortisone group, *versus* 28.8% mortality in the placebo group).⁵⁶ APPROCCHESS, also published in 2018, was initially conceived of as a 2 × 2 trial randomizing patients with vasopressor-dependent shock to either corticosteroids (with fludrocortisone) or no corticosteroids and activated protein C or no activated protein C.⁵⁷ Activated protein C was withdrawn from the market during the recruitment period, and thus the study was converted to low dose corticosteroids *versus* placebo in septic shock; 1241 patients were recruited. There was a statistically significant 6% reduction in mortality at 90 days (primary outcome, 43% hydrocortisone/fludrocortisone *versus* 49.1% placebo). The substantially higher rate of death overall in the APPROCCHESS trial suggests a sicker patient population was enrolled than in the ADRENAL trial. Of note, both studies demonstrated improvement in secondary outcomes of resolution of shock and earlier liberation from mechanical ventilation.

Differences in the trials might explain the lack of uniformity in results, including differences in illness severity, timing of initiation of steroid therapy with respect to onset of sepsis or septic shock, dosing of the steroids with or without fludrocortisone, and the proportion of relative corticosteroid deficiency patients present in each cohort. Currently, the Surviving Sepsis Campaign guidelines recommend the use of adjunctive glucocorticoids in patients with septic shock refractory to

fluid resuscitation,¹⁸ and the more recent studies support the notion that the potential benefits of low-dose hydrocortisone might outweigh the risks especially in a sicker patient population.⁵⁰

Procalcitonin

Procalcitonin is a precursor of calcitonin that is undetectable in healthy states but is upregulated by the cytokines that are secreted in bacterial infections.⁵⁸ In patients with suspected sepsis or septic shock, it is not advised to use procalcitonin to guide decision-making regarding initiation of antibiotics, but, in some circumstances, procalcitonin might be helpful in guiding de-escalation of antibiotic use. Several trials have investigated the use of procalcitonin to guide duration of antimicrobial therapy in sepsis. PRORATA randomized 621 patients with suspected bacterial infection to standard of care *versus* early de-escalation of antibiotic therapy based on procalcitonin levels. In the intervention arm, antibiotics could be discontinued when procalcitonin dropped below 0.5 µg/ml or had been reduced from 80% of the peak serum value. There was less antibiotic use in the intervention arm, as well as a trend towards increased mortality in the intervention arm, though this did not reach the level of significance.⁵⁹ ProGUARD randomized 400 patients to either standard of care or a more conservative cut-off for de-escalation of antibiotics; in this trial antibiotics could be discontinued if procalcitonin fell below 0.1 µg/ml or a 90% reduction from peak serum value.⁶⁰ This trial found a nonsignificant reduction in antibiotics in the intervention arm and no differences in mortality. Finally, SAPS randomized 1575 patients to the cut-offs used in PRORATA *versus* standard of care; this study found a significant reduction in days on antibiotics in the procalcitonin arm, as well as a 5% reduction in mortality in the procalcitonin arm.⁶¹

Thus, there is a range of opinion regarding the appropriate use of procalcitonin in critical illness. As severely immunocompromised patients have not been adequately studied in these trials, it has not been advised to guide therapy using procalcitonin in this group of patients. Additionally, certain other patients might require long-term antibiotics, such as those with *Staphylococcus aureus* bacteremia, endocarditis, osteomyelitis, joint infections, mediastinitis, liver/brain abscesses, chronic pancreatitis, etc.; and these

patients should not have antibiotic decisions guided by procalcitonin levels. Of note, false positive procalcitonin levels can occur (e.g. from non-infectious inflammatory conditions such as trauma, pancreatitis, burns, etc.), and false negative procalcitonin levels can occur (e.g. early in the course of illness or in the setting of walled off infectious such as abscesses). In general, in situations where one might consider de-escalating antibiotics guided by procalcitonin levels, the patients should be clinically improving, and an alternate diagnosis should be more apparent. It is important to note that if procalcitonin levels are used as a clinical decision aid, they should never override clinical judgement.⁶²

Vitamin C

There are reasons for interest in vitamin C as a therapy in sepsis, as patients with sepsis may be deficient in vitamin C.⁶³ A randomized controlled trial in critically ill surgical ICU patients showed a decrease in multi-organ failure in patients treated with vitamin C and vitamin E.⁶⁴ A phase I study of vitamin C in sepsis found a favorable safety profile and improvement in SOFA scores with escalating doses of vitamin C in a cohort of 24 patients.⁶⁵ A 2017 retrospective study by Marik and colleagues compared patients treated with vitamin C, hydrocortisone, and thiamine with historical controls, and found significantly decreased mortality in the intervention arm.⁶⁶ However, the Marik study has significant limitations, including the single center studied, the nonrandomized intervention, and the use of a historical control. Two prospective trials are currently underway that may shed more light on the efficacy of vitamin C as a treatment for sepsis.^{67,68}

Modulating the immune system

For decades, it has been thought that dampening the robust pro-inflammatory cascade generated early in sepsis might represent an optimal therapeutic strategy. However, attempts to dampen inflammation have failed to improve sepsis outcomes, including inhibiting innate immunity by antagonizing toll-like receptors,⁶⁹ or directly reducing the activity of pro-inflammatory cytokines by binding tumor necrosis factor,⁷⁰⁻⁷² or interleukin 1.⁷³ It has further been appreciated that an early pro-inflammatory response might be

followed by a later immune suppressive phase, including the concept of T-cell ‘exhaustion’ as indicated by up-regulation of Programmed Death Ligand-1 (PD-L1).⁷⁴ Immune checkpoint inhibitors are being considered for their potential to augment the host response in sepsis to reverse T-cell exhaustion by inhibiting PD-L1, though no trial in human subjects has yet been published.⁷⁵ A theoretical risk of such an approach is that pneumonitis has been well-described as a potential complication of checkpoint blockade in cancer treatment.⁷⁶ Along these lines, it has been recently observed that alveolar macrophages isolated from ARDS patients that have higher PD-L1 expression correlate with improved ARDS outcomes,⁷⁷ supporting the notion that decreasing PD-L1 expression in sepsis would need to be carefully considered. Other proposed immunomodulatory strategies include GM-CSF,⁷⁸ interferon gamma,⁷⁹ and mesenchymal stem cells,⁸⁰ though there are not yet definitive data in humans for these approaches.

More recently there has been consideration that it might be necessary to ‘titrate’ the inflammatory response optimally for a given patient at a given time during sepsis. One such approach might include measuring levels of various cytokines with the goal of modulating expression in a targeted manner based upon a septic individual’s profile at any point in time⁸¹; however, the turnaround time for these types of assays in the setting of rapidly changing inflammatory states and clinical conditions would prove difficult. As an example of an attempt to consider bedside immunophenotyping, electrical cell profiling has been tested in pre-clinical sepsis models in real-time to rapidly measure immune cell activation with small blood volumes, and might be one of a number of approaches stratify patients with sepsis into various immunophenotypic groups that might permit targeted therapy.⁸² However, more understanding of which pathways to target, how best to target them, and at which time points of sepsis are ongoing areas of investigation.

Sepsis specific education and resources

Education regarding the signs, symptoms, and optimal treatment of sepsis can reduce mortality. Educational initiatives should extend beyond physicians, as allied health professionals are often the first providers who might identify

patients with sepsis early in their course.⁸³ Pocket cards reviewing sepsis guidelines that can be carried easily have been shown to improve knowledge of sepsis diagnosis and management among physicians.⁸⁴ A retrospective analysis of outcomes after a sepsis simulation program at a single Korean center showed improved compliance with sepsis bundles and a decrease in mortality.⁸⁵ Sepsis response teams, composed of specially trained nurses, physicians, respiratory therapists, and pharmacists, have been shown to improve compliance with guidelines and reduce sepsis mortality.⁸⁶

Adjunctive therapies

Other therapeutic/management strategies that have been shown to improve outcomes in sepsis and septic shock are reviewed in detail elsewhere. It is likely that comprehensive multidisciplinary management is important for optimal ICU outcomes for patients with sepsis and/or septic shock. For example: patients randomized to a liberal glucose goal of ≤ 180 mg/dL had lower mortality in a randomized trial compared with those randomized to intensive control with a goal of 81–108;⁸⁷ management of coincident ARDS with low tidal volumes reduces mortality;⁸⁸ conservative fluid management in patients with ARDS was shown to reduce the duration of mechanical ventilation;⁸⁹ and protocolized central venous catheter insertion and care have been shown to reduce catheter associated blood stream infections.^{90,91}

Conclusion

The cornerstones of management of sepsis remain early diagnosis, early administration of appropriate antibiotics, support of perfusion with targeted fluid resuscitation and vasopressors, and adequate source control (summarized in Figure 1). Low-dose hydrocortisone might be beneficial especially in sicker sepsis patients with refractory shock. Despite decades of research, there still exist no targeted biologics for diagnosis, monitoring, or treatment of septic patients. Future research should aim to further understand the biological basis of sepsis and septic shock so that targeted therapies might be developed, and to further and more finely phenotype patients with sepsis such that groups of patients that might benefit from a particular therapy might be more readily identified.

Timeline of critical management aspects of sepsis and septic shock, from time of presentation

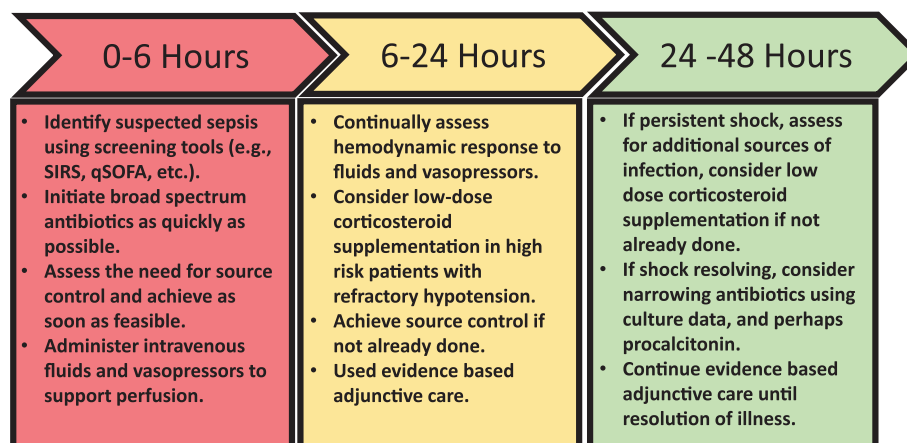


Figure 1. A schematic highlighting critical aspects of management of sepsis and septic shock.

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J.V. and R.M.B. designed, conceived, wrote, and edited the manuscript.

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Ethical statement

Our study did not require an ethical board approval because it did not contain human or animal trials.

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