Sepsis in 2018: a review

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Abstract

Sepsis is responsible for tremendous morbidity, mortality and healthcare expenditure worldwide. Recently, the conceptualization of sepsis has shifted away from one based upon the inflammatory response to infection to one based upon a dysregulated immune response and resulting organ dysfunction. Revised definitions of sepsis and septic shock have been proposed in order to improve the specificity of the diagnostic criteria and to provide tools to facilitate accurate and timely (i.e. early) diagnoses at the bedside. The crux of sepsis management remains *early* identification and diagnostic testing, *early* antimicrobial therapy, and *early* haemodynamic resuscitation. The most recent guidelines recommend that first steps in this process should take place within 1 hour from when sepsis is suspected. Additional important new elements in the most recent sepsis management guidelines include the use of dynamic parameters to assess fluid responsiveness, a conservative fluid strategy following initial resuscitation (with 'de-resuscitation' when possible), serial re-assessments of haemodynamic status, and adaptable treatment plans. This article provides a summary of the most recent clinical evidence and professional guidelines for the diagnosis and treatment of the sepsis in the critical care setting.

Keywords Critical care; intensive care; sepsis; septic shock

Royal College of Anaesthetists CPD Matrix: 2C03

Learning objectives

After reading this article, you should be able to:

- define sepsis and septic shock (Sepsis-2 *and* Sepsis-3)
- describe clinical criteria required for the early diagnosis of sepsis
- formulate an initial treatment plan for the septic patient in a critical care setting
- describe secondary and adjunctive therapies presently available for refractory sepsis

Introduction

Every year in the United Kingdom, an estimated 250,000 cases of sepsis occur, claiming at least 46,000 lives. It constitutes a staggering economic burden on the National Health Service (NHS) of £1.5–2.0 billion each year. Further, an aggregated annual cost to society from its long-term effects on survivors is believed to be £15.6 billion.[1] Robust epidemiological assessments project that there are 31.5 million cases of sepsis annually worldwide, resulting in approximately 5.3 million deaths per year. Hospital mortality rates for patients with sepsis are estimated to be as high as 35.3%.[2] More timely and accurate recognition of at-risk patients is essential to improving patient care. To that end, this article will review recent changes in the definitions and clinical guidelines for the treatment of sepsis.

Pathophysiology of sepsis

At its onset, sepsis manifests as an overwhelming release of inflammatory mediators (sometimes referred to as 'cytokine storm') in response to an infection. The immune responses to infection can be correlated with national defenses: components of the innate immune system or 'citizens' (epithelial cells, macrophages, mast cells, innate lymphocytes) at the site of pathogen exposure activate and recruit circulating immune cells or 'troopers' (neutrophils, NK cells, dendritic cells, platelets, monocytes, eosinophils). These cells have pathogen-recognition receptors (PRRs) on their surface which bind to, and are activated by, pathogen-associated molecular patterns (PAMPs) on bacterial cell walls or damage-associated molecular patterns (DAMPs) – host biomolecules released when danger is sensed from a pathogen, burn, trauma, etc. This receptor binding initiates an intracellular signaling cascade resulting in the activation of cytosolic transcription factors such as NF-kB and activator protein 1 (AP-1), which in turn leads to the production of several acute phase reactants, among them cytokines, coagulation factors and inducible nitric oxide synthetase, thus initiating the immuno-inflammatory cascade. A subsequent chain reaction involves the activation of even stronger 'armed forces', the adaptive immune response. This explosive activation and resultant immune 'cytokine storm' is believed to be the causative pathway for septic shock.[3]

The end response to an infection is often a combination of pro- and anti-inflammatory cascades. Once infection resolves, a balance is established between immune up-regulating and down-regulating processes, and immune memory is generated to protect against future exposures. However, when the initial response is excessive or dysregulated, this balancing process itself can become dysfunctional. As sepsis persists, by about 24–48 hours a shift towards an anti-inflammatory state is observed and patients develop features consistent with immunosuppression. This phase is known as sepsis-induced immunoparalysis.[4] The majority of septic shock-related deaths occur during this immunoparalysis phase. These patients are often not able to clear the initial infection and, in addition, are predisposed to new infection

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from nosocomial pathogens. T-cell exhaustion, apoptosis and anergy are now recongnized immunosuppressive mechanisms observed in patients with fatal sepsis.[5,6]

Definitions

Over the course of the last three decades, considerable effort has been expended in improving the recognition, categorization, and the algorithmic treatment of sepsis. From the early 1990s until recently, sepsis was diagnostically defined as a suspected infection accompanied by a pronounced Systemic Inflammatory Response Syndrome (SIRS) (See Table 1). Patients were then further categorized as having sepsis, severe sepsis or septic shock based on organ dysfunction and fluid responsiveness. Though this approach became critical care dogma, it failed to detect many cases of sepsis – as many as one in eight for severe sepsis.[7]

The Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) sought to revise the definition of sepsis by employing recent advancements in the understanding of sepsis pathophysiology. The Third International Consensus Definitions for Sepsis and Septic Shock ('Sepsis-3'), released in 2016, recongnized sepsis as more than an inflammatory response and acknowledged that both pro- and anti-inflammatory processes, as well as major alterations in non-immunologic systems play a role in the disease process.[4] After eliminating the term 'severe sepsis', sepsis was re-defined as 'life-threatening organ dysfunction caused by a dysregulated host response to infection'. The statement further defined septic shock as a 'subset of sepsis in which profound circulatory failure, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone'. For a comparison of differences between the Sepsis-2 and Sepsis-3 definitions, please refer to Table 2.

In addition to these conceptual definitions, the consensus committee also established a set of practical clinical guides to facilitate diagnosis at the bedside. The authors selected the Sequential Organ Failure Analysis (SOFA) assessment to identify organ dysfunction (see Table 3). The clinical criteria for the diagnosis of sepsis were modified to a SOFA score of 2 or more (or a change of $\geq$2 in SOFA score), *plus* persistent hypotension requiring the use of vasopressors to maintain a MAP >65 mmHg and a serum lactate >2 mmol/L that persists despite adequate fluid resuscitation (Table 4).

The SOFA score requires the knowledge of multiple laboratory values (i.e. platelets, bilirubin, creatinine) that are not readily available at the bedside outside of an acute care setting. Thus, the more cumbersome SOFA score was adapted to a quick SOFA ('qSOFA') to allow for simple, rapid assessments in the prehospital, clinic, or emergency department environment (see Box 1). Based upon a cohort study of nearly 150,000 patients with suspected infection, the Sepsis-3 authors determined that the qSOFA assessment was more *predictive* of the development of sepsis in at risk patients outside the ICU setting than the traditional SIRS criteria.[8]

Systemic inflammatory response syndrome[a]

Two or more of the following:

Temperature	<36°C or >38°C
Heart rate	>90/min
Respiratory rate	>20/min OR $PaCO_2$<32 mmHg
WBC	<4,000/mm^3 OR >12,000/mm^3, or 10% bands

[a] one RC, Balk RA, Cerra FB et al. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 1992; 20 (6):864–874.

Table 1

Comparison of Sepsis-2 and Sepsis-3[a]

	Sepsis-2	Sepsis-3
Publication year	2001	2016
Mechanism (pathophysiology)	Physiological inflammatory response (SIRS) to infection	Dysregulated immune response to infection
Spectrum	SIRS → sepsis → severe sepsis → septic shock → MODS	Sepsis → septic shock
Predictive validity for in-hospital mortality (Area under the curve, p<0.001)[3]	0.64 (95% CI, 0.62–0.66)	0.74 (95% CI, 0.73–0.76)
Sensitivity/specificity	↑ Sensitivity ↓ Specificity	↓ Sensitivity ↑ Specificity
Definition of septic shock	Acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes	Subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality
Practical considerations	Three of four SIRS criteria obtainable at bedside without need for laboratory testing	Multiple laboratory test results required to calculate SOFA score; qSOFA can be used as substitute prior to test availability

[a] Singer M, Deutschman CS, Seymour CW et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; 315 (8):801–810.

Table 2

Sequential [Sepsis-Related] Organ Failure Assessment Score (SOFA)[a]

System	Score 0	1	2	3	4
Respiratory					
PaO_2/FiO_2, mmHg	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation					
Platelets, x $10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular					
	MAP≥70 mmHg	MAP<70 mmHg	Dopamine<5 or dobutamine (any dose)[b]	Dopamine 5–15 or norepinephrine ≤0.1 or epinephrine≤0.1[b]	Dopamine>15 or norepinephrine>0.1 or epinephrine>0.1[b]
Central nervous system					
Glasgow Coma Scale[c]	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg/dL	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
Urine output, mL/day				<500	<200

Abbreviations: FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure.

[a] Vincent JL, Moreno R, Takala J et al. Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996; **22** (7): 707–710.

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3 to 15; higher score indicates better neurologic function. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. 1974; **2**: 81–84.

Table 3

Sepsis-3 Criteria for Sepsis/Septic Shock[a]

Sepsis	qSOFA≥2 plus evidence of infection
Septic shock	Sepsis plus persistent hypotension requiring administration of vasopressors to maintain a MAP>65 mmHg and a lactate >2mmol/L despite adequate fluid resuscitation

[a] Adapted from: Singer M, Deutschman CS, Seymour CW et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; 315 (8):801–810.

Table 4

Quick Sequential Organ Failure Analysis (qSOFA) score[a]

qSOFA criteria: ≥ 2 of the following

Respiratory rate >22/min
Change in mental status
Systolic blood pressure <100 mmHg

[a] Adapted from: Singer M, Deutschman CS, Seymour CW et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).*JAMA*.2016; 315 (8):801–810.

Box 1

It should be noted that the new definitions proposed by Sepsis-3 have not been universally accepted. Almost immediately, investigators attempted to compare SIRS and qSOFA as sepsis screening modalities. In a recently published study, Fernando et al. performed a retrospective meta-analysis comparing the prognostic accuracy of SIRS to qSOFA and found qSOFA to have poor sensitivity and moderate specificity to predict short-term mortality; SIRS criteria displayed superior sensitivity.[9] Though Sepsis-3 incorporated the qSOFA methodology, some clinicians still prefer SIRS and this remains an active area of discussion in the critical care community.

Management

Irrespective of debates over the definition of sepsis, the cornerstone of effective treatment is indisputably early identification and aggressive, targeted management. Successful treatment requires fluid resuscitation with a focus on perfusion and early administration of antibiotics. The most recent 2018 Surviving Sepsis Campaign (SSC) Bundle Update introduced the '1-hour Bundle'.[10] This new bundle combines elements of the prior 3- and 6-hour Bundles into an algorithm that emphasizes the *immediate* treatment of septic patients. The first elements of the bundle are diagnostic: measuring a lactate level and obtaining blood cultures prior to administration of antibiotics. The remainder of the bundle addresses management: early antimicrobial administration, fluid resuscitation, and if required, vasopressor support (see Box 2).

Surviving Sepsis Campaign 1-hour Bundle[a]

- Measure lactate level (follow serial measurements if initial level >2mmol/L)
- Obtain blood cultures prior to administering antibiotics
- Administer broad spectrum antibiotics
- Begin rapid administration of 30mL/kg of crystalloid for hypotension or lactate ≥4mmol/L
- Start vasopressors if patient is hypotensive during or after fluid resuscitation to maintain a MAP ≥65 mmHg

[a] Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive care medicine. 2018 Jun 1; 44 (6):925–8.

Box 2

Early antimicrobial therapy and source control

For patients with presumed sepsis, early empiric broad-spectrum antibiotic therapy should be initiated within 1 hour of presentation. Ideally, microbiologic data should be obtained prior to administering antibiotics. However, if obtaining cultures will delay antibiotic administration, then antibiotic therapy should always take priority. In multiple studies, the prompt administration of antibiotics was associated with improved survival.[10,11] The selection of appropriate empiric antibiotic therapy is essential for decreasing mortality in septic patients and should be guided by clinical presentation and local antimicrobial resistance patterns, as well as the patient's risk factors for particular organisms (see Table 5).[11] Comorbidities contributing to chronic illness (e.g. human immunodeficiency virus, combined variable immunodeficiency, diabetes mellitus) and the presence of invasive medical devices (e.g. central venous catheters, urinary catheters) should also be weighed when selecting initial antibiotic regimens.

When the source of infection is unclear, empiric coverage should be initiated. For the majority of patients, antimicrobial coverage should include either an extended spectrum beta lactam, a third or fourth generation cephalosporin, or a carbapenem. Additional consideration should be paid to meticillin-resistant *Staphylococcus aureus* (MRSA) risk factors and if present, empiric vancomycin administration is advised. Widespread use of combination therapy, the use of multiple antibiotics with different pharmacodynamic profiles and mechanisms of action to treat the same organism, is a topic of some debate, though early studies reported a synergistic effect with the addition of an aminoglycoside to a beta-lactam[12] and later studies assessed the addition of a fluoroquinolone. Combination therapy *has* been shown to improve survival in the most critically ill patients (i.e.: in septic shock where the mortality risk is greater than 25%).[13] In the appropriate clinical context (e.g. suspected influenza), empiric anti-viral therapy is often appropriate. Likewise, clinical scenarios that include immunosuppression, total parenteral nutrition, or recent abdominal surgery may justify the use of empiric anti-fungal therapy. Once microbial data are available, prompt de-escalation of therapy is *imperative*.

Source control, a crucial element of proper sepsis treatment, may require more invasive interventions than antimicrobial administration alone. The removal of potentially infected invasive devices is highly recommended; this includes urinary and central venous catheters. Prompt consultation with surgical or interventional radiology services is advised to address scenarios such as an empyema, joint infection, cholecystitis or intra-abdominal catastrophe. Generally, the least invasive intervention capable of providing source control is the preferred option. A multidisciplinary approach to early intervention (<6 h) can improve patient mortality.[14]

Fluid resuscitation

Prompt fluid resuscitation should be initiated upon the diagnosis of sepsis. Current guidelines strongly recommend the initiation of

Risk factors for select organisms

Pseudomonas aeruginosa **(and other resistant Gram negative rods)**	**MRSA**	**VRE**	**Invasive candidiasis**

Community acquired:
• IV antibiotic use within 90 days
• Colonization with MDROs
Hospital acquired:
• IV antibiotics within 90 days
• Five or more days of hospitalization prior to onset
• Requiring acute renal replacement therapy
• Septic shock
• Colonization with MDROs
	• Colonization with MDROs
	• Recent MRSA infection
	• Known MRSA colonization
	• Purulence or abscess of the skin or IV access site
	• Severe rapidly progressive necrotizing pneumonia
		• Liver transplant
		• Known colonization
		• Prolonged use of broad spectrum antibiosis
		• Profound immunosuppression
			• Central venous catheter
			• Broad spectrum antibiotics
			• Plus one of the following
			  • Parenteral nutrition
			  • Dialysis
			  • Recent abdominal surgery
			  • Necrotizing pancreatitis
			  • Immunosuppressive agents

Adapted from Derensinski, Stan. 'Severe Sepsis and Septic Shock Antibiotic Guide.' Stanford Antimicrobial Safety and Sustainability Program. Stanford Health. May 2017. http://med.stanford.edu/bugsanddrugs/guidebook/_jcr_content/main/panel_builder_1454513702/panel_0/download_1586531681/file.res/Sepsis%20ABX%202017-05-25.pdf

Table 5

the infusion of 30 mL/kg of IV crystalloid fluid within 1 hour of sepsis identification if hypotension is present.[10] However, the type of fluid to be used for resuscitation remains an active area of debate. In 2004, the SAFE trial compared clinical outcomes in critically ill patients receiving volume resuscitation with either normal saline or albumin.[15] No significant difference in all-cause mortality was noted between the two groups, though a sub-group analysis did show unfavourable outcomes when albumin was administered to patients with traumatic brain injury. The combination of the increased expense of albumin infusion and an absence of data to support a clear benefit led the Surviving Sepsis Campaign (SSC) to recommend crystalloids as the volume resuscitation agents of choice.

Which crystalloid to use is also a matter of active debate, but as more data become available, balanced salt solutions such as lactated Ringer's or PlasmaLyte are likely to emerge as the recommended options. For example, a recently completed trial of nearly 8000 patients found the use of balanced crystalloids in critically ill patients slightly decreased mortality, the use of renal replacement therapy, and persistent renal dysfunction when compared to 0.9% saline solution.[16]

While adequate resuscitation is essential, fluid overload is associated with increased mortality,[17] making perfusion assessment an essential part of the treatment algorithm. Careful attention to fluid management with *de-resuscitation* 24–48 hours after successful resuscitation decreases the ICU length of stay and increases ventilator-free days.[18]

Perfusion assessment

Once initial fluid resuscitation has been completed, frequent reassessment of systemic perfusion using dynamic variables is recommended. While prior iterations of the SSC recommended the use of early goal-directed therapy-based resuscitation protocols, where perfusion was assessed by a combination of central venous pressure (CVP) and central venous oxygen saturation levels, the most recent SSC guidelines favour alternative dynamic measures.[19] Techniques such as passive leg raising maneuvers, pulse pressure variation, and point-of-care ultrasound assessments are now recommended as means to gauge whether a patient requires further volume resuscitation. These dynamic assessments and reassessments of perfusion are now regarded as essential to improving patient outcomes.

Serum lactate continues to play a role as an indirect marker of tissue perfusion. The SSC guidelines recommend a serum lactate assay at baseline, and, if elevated, serial monitoring until normalization. Several randomized controlled trials using lactate guided resuscitation have shown significant reductions in mortality.[20,21]

Vasopressors

Mean arterial pressure (MAP) is the driving factor behind systemic perfusion. When hypotension persists despite adequate IV fluid resuscitation, vasopressors should be administered. At present, the SSC recommends noradrenaline/norepinephrine as the first-line vasopressor.[22] If a second agent is necessary to achieve MAP goals, vasopressin or adrenaline/epinephrine are the recommended options.

Patients with septic shock are hypothesized to have a 'relative vasopressin deficiency', meaning that levels of vasopressin are lower than expected for a shock state.[23] The use of low-dose vasopressin or terlipressin is an effective treatment for refractory shock. Furthermore, the addition of vasopressin has been noted to have a 'dose sparing' effect on norepinephrine requirements, potentially decreasing the risk of tachyarrhythmia[24,25] and other catecholamine-associated side-effects.

In low doses, adrenaline/epinephrine is an inotrope, but at higher doses it demonstrates vasoconstrictive properties. A head-to-head comparison of norepinephrine to epinephrine in septic shock showed no difference in mortality, but increase in adverse events in the epinephrine arm.[26] It is important to note that epinephrine infusions often cause hyperlactatemia, limiting the usefulness of lactate clearance as an indicator of response to therapy.

The choice between adrenaline/epinephrine and vasopressin as a second-line agent should be based upon the patient's current hemodynamic status and underlying physiology, particularly the presence of (or risk for) tachyarrhythmias or elevated lactate levels.

Previously considered the first-line vasopressor for septic shock, dopamine has fallen out of favour. A 2015 meta-analysis compared the use of norepinephrine to dopamine in patients with septic shock and found decreased all-cause mortality in the norepinephrine treated patients.[27] The abundance of data on its arrhythmogenic properties in conjunction with a less favourable hemodynamic profile overall make dopamine a less desirable choice in the treatment of septic shock. Consequently, it should be reserved for a select patient population (e.g. septic patients with bradycardia, low risk of tachycardia).[22,28]

There are little data about the use of phenylephrine in patients with septic shock. Due to its potential to cause splanchnic vasoconstriction, and an absence of robust clinical data supporting its safety in septic shock, its use should be limited in patients with sepsis.[22]

The ATHOS-3 trial presented a new option for management of vasodilatory shock – angiotensin II (ATII). In this recently published multicenter randomized controlled trial (RCT) of patients with catecholamine refractory vasodilatory shock, the group treated with ATII demonstrated a significant increase in blood pressure, and no significant difference in adverse events was noted between the groups.[29] Though large scale clinical data are not available at this time, ATII appear to be a promising therapy for catecholamine refractory shock.

A subset of patients with septic shock will develop septic cardiomyopathy. These patients typically have little cardiac reserve at baseline and are unable to generate a compensatory cardiac output during vasodilatory shock. If cardiac output remains low despite use of vasopressors, initiation of inotropic therapy is appropriate. The Surviving Sepsis Campaign Guidelines recommend dobutamine as the preferred inotrope, though data show similar improvements in cardiac output with the use of epinephrine as a single agent as with dobutamine paired with norepinephrine.[10]

Diagnostic techniques

Microbiological cultures

Positive blood cultures are demonstrable evidence of systemic infection. If sepsis is suspected, current guidelines recommend

drawing two sets of blood cultures, both aerobic and anaerobic. However, blood culture yield is variable and is dependent upon sampling technique. Care must be taken to adequately prepare the skin with antiseptic agent and to inoculate each bottle with a minimum of 10 mL of blood. Ideally, cultures should be obtained prior to the administration of antibiotics. Cultures of other bodily fluids should also be obtained as clinically indicated (e.g. sputum, urine, cerebrospinal fluid, etc.).

Lactate

Elevated serum lactate is a marker of disease severity in sepsis. The etiology of the rise in lactate is multifactorial, including anaerobic metabolism resulting from inadequate oxygen delivery and accelerated aerobic glycolysis. Several randomized controlled trials reported that a lactate-guided resuscitation strategy in patients with septic shock reduced mortality.[22] As such, measurement of lactate is a mainstay of sepsis treatment protocols and is included in the current clinical criteria for the diagnosis of septic shock.

Biomarkers

A myriad of novel biomarkers (e.g. supar, presepsin, cell-free plasma DNA) are under study with the aim of improving diagnostic precision, more accurate prognostication, and ultimately, monitoring treatment response. However, most have not been shown to have the sensitivity, specificity, or cost-efficacy necessary to justify use in clinical practice.[30]

Procalcitonin (PCT) is the most studied sepsis biomarker.[31] A precursor to the hormone calcitonin, levels are routinely elevated in the setting of systemic bacterial infection. Thus far, studies show procalcitonin to be useful in decreasing the duration of antibiotic treatment.[32] Elevations of PCT can be seen in uninfected patients, however, particularly in patients with renal disease. Based upon available data, the SSC suggests using procalcitonin to limit or discontinue antibiotic therapy only. An elevated procalcitonin in itself is insufficient to determine the initiation (or not) of antibiotics.[22]

Molecular techniques

Identifying and treating the offending organism in a timely manner is often a challenge. Conventional blood cultures can take up to 72 hours to provide a definitive result. Recently developed molecular techniques can detect pathogens far more quickly. Ongoing evaluations of pathogen identification techniques using multiplex polymerase chain reaction (PCR), PCR/electrospray ionized mass spectroscopy (ESI MS), and functionalized nanoparticles coupled with magnetic resonance have shown promise with the capability of identifying organisms in under 6 hours with reasonable sensitivity and specificity. Further studies and cost analyses will determine whether these techniques are incorporated into general clinical practice, but in the near future these techniques may very well obviate the need for conventional blood cultures.[33]

Adjunctive therapies

Steroids

Despite the physiological plausibility for the effectiveness of steroids in septic shock, the data are conflicting on their efficacy in clinical practice. In 2015, a review by Annane et al. analysed 33 trials and concluded that corticosteroids generally reduce mortality among patients with sepsis (though the evidence was rated as low quality).[34] Based on this, the 2016 Surviving Sepsis Campaign Guidelines recommended 200 mg per day of IV hydrocortisone for patients who have persistent circulatory failure despite adequate fluid resuscitation and vasopressor therapy. However, the role of steroids in septic shock does remain an active area of research. The recently published ADRENAL trial (ADjunctive corticosteroid tREatment iN criticAlly ilL) randomized critically ill patients to receive hydrocortisone 200mg/day versus placebo. No difference in mortality was noted but there was a significant improvement in reversal of shock, length of stay in ICU, ventilator-free days and fewer blood transfusions.[35] Conversely, a multicentre, randomized controlled trial administering hydrocortisone plus fludrocortisone (versus placebo) to patients in septic shock *did* find a reduction in all-cause mortality in the treatment group.[36] Much like the evidence, the critical care community remains divided on the use of steroids in septic shock.

Vitamin C (±thiamine)

Vitamin C as an adjunctive therapy for sepsis has received considerable media attention. At present, while the results from a single centre retrospective trial using vitamin C with thiamine and glucocorticoids are intriguing,[37] there are no multicentre, randomized controlled trials to support the routine use of vitamin C or thiamine in patients with sepsis.[38]

Blood purification techniques

Endotoxin is circulating in 50% of patients in septic shock and is associated with poor outcomes.[39] The EUPHRATES trial attempted to neutralize endotoxin via a polymyxin fibre in a hemoperfusion device.[40] EUPHRATES was the largest RCT to study this technology, but was terminated early due to failure to achieve the primary endpoint. Other techniques, such as extracorporeal plasma filtration to remove pro- and anti-inflammatory mediators from the bloodstream, are under evaluation.[41] While the concept remains appealing, at this time data are lacking to support its efficacy.

Glycaemic control

Glycaemic control in sepsis is a much-debated topic. On one hand, hyperglycaemia can exert an immunosuppressive effect diminishing the body's ability to mount a competent immune response. On the other, the anti-inflammatory effects of insulin may inhibit cellular autophagy and negatively impact a patient's capacity to clear infection.[42]

Evidence shows that severe hyperglycaemia in patients with sepsis is associated with increased 30-day mortality.[43] On the other hand, the NICE-SUGAR trial, a large, multicentre, randomized controlled trial compared intensive insulin control (81−108 mg/dL) to conventional insulin control (<180 mg/dL), and reported increased mortality due to hypoglycaemia with intensive insulin therapy.[44] With both hyper- and hypoglycaemia associated with adverse outcomes, current recommendations are to start insulin after blood glucose levels exceed 180mg/dL (10 mmol/L) with the goal of maintaining levels less than 180mg/dL. There is no specific lower threshold target, but avoidance of hypoglycaemia and wide swings in glucose levels is advised.

Anticoagulants (including thrombomodulin and heparin)

Activated protein C (APC) was once thought to mediate the systemic inflammatory response of sepsis by promoting fibrinolysis and inhibiting thrombosis, and initial trials (PROWESS) indicated a survival benefit when administered to patients with very severe sepsis. In both the 2004 and 2008 SSC guidelines, APC was a recommended therapy. However, with the publication of PROWESS-SHOCK in 2012, which showed no benefit to APC use in sepsis, it was withdrawn from the market by the manufacturer.[45]

The use of thrombomodulin in the setting of sepsis with disseminated intravascular coagulation (DIC) is well established in Japan and is presently undergoing late phase testing in the USA and Europe. Other anticoagulants, such as antithrombin and heparin have been studied, but neither can be recommended as part of a routine treatment at this time.[46,47]

Intravenous immunoglobulin

Another therapy that has been studied for many years as a treatment for sepsis is purified intravenous immunoglobulin (IVIG). Thought to mitigate the inflammatory response and augment immune mechanisms, IVIG has the potential for therapeutic modulation of both pro- and anti-inflammatory processes. To date, published data on IVIG use in sepsis have been contradictory, but a recently published meta-analysis of IVIG use in septic shock suggested a potential survival benefit.[48] Regardless, IVIG is not currently recommended as a therapeutic agent by the SSC.

Conclusions

Sepsis and septic shock are leading contributors to worldwide morbidity and mortality. Though the Sepsis-3 definitions are not without controversy, they seek to expand upon our growing understanding of sepsis as a dysregulated immune response as opposed to solely an inflammatory process. Regardless of changes to the definition, early recognition and prompt management such as the implementation of the recently published 1-hour Bundle are essential to improving patient outcomes. The core elements of any treatment algorithm are much the same: antibiotics, source control, intravenous fluid resuscitation and vasopressors, tempered with the recognition that sepsis is not a static process and that frequent reassessment and adaptation of the treatment plan is essential. Many potential adjunctive therapies and novel diagnostic techniques are on the horizon, though more research is required to define their role in routine clinical practice. ◆

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