Sepsis – Frontiers in diagnosis, resuscitation and antibiotic therapy

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Expected resuscitation and infection control interventions to improve the management and outcomes in patients with sepsis

Abstract

Sepsis is a major growing global burden and a major challenge to intensive care clinicians, researchers, guideline committee members and policy makers, because of its high and increasing incidence and great pathophysiological, molecular, genetic and clinical complexity. In spite of recent progress short term mortality remains high and there is growing evidence of long term morbidity and increased long term mortality in survivors of sepsis both in developed and developing countries. Further improvement in the care of patients with sepsis will impact upon global health.

In this narrative review, invited experts describe the expected challenges and progress to be made in the near future. We focus on resuscitation (fluids, vasopressors, inotropes, blood transfusion and hemodynamic targets) and infection control (antibiotics and infection biomarkers) as these areas are key, if initial management and subsequent outcomes are to be improved in patients with sepsis.

Introduction

Sepsis remains a major challenge to intensive care clinicians, researchers and policy makers, because of its high incidence and mortality and ongoing challenges in early identification [1].

Sepsis is a syndrome, i.e. an artificial construct created for operational purposes. This facilitates identification, triage, and activation of specific interventions, prognostication, communication with patients, families and care-givers, epidemiology and coding. The ability to create a sepsis construct with face validity derives from the many clinical and biological similarities shared by patients suffering from a wide range of major infections (e.g. pneumonia, peritonitis, meningitis, pyelonephritis and necrotizing fasciitis). Once the innate immune system is activated there are major alterations in multiple systems that may lead to multiple organ failure and death [2]. Sepsis remains the commonest cause of emergency admission to ICU globally. It is responsible for approximately 11% of all admissions to ICUs in high income countries, often in association with older age, comorbidities and the use of immunosuppressive medications. Sepsis affects between 3 to 10 per 1000 population per year in such countries and carries an associated mortality of between 18-35% [6,7].The epidemiology of sepsis in low and middle income countries remains less well understood [1]. The mortality of sepsis appears to have progressively decreased over the last decades [6, 7], despite observations that are confounded by changes in coding within administrative databases [8].

In this narrative review, experts invited by the editorial board of Intensive Care Medicine, share their insights into key aspects of sepsis diagnosis and specific and supportive treatment with the aim of providing a state-of-the art position at this time. This will generate debate, indicates areas of imminent progress and contribute to the research agenda.

Definitions

The first definitions of sepsis, severe sepsis and septic shock were described in 1992 [9]. These were superseded in early 2016 by new definitions (Table 1) developed by an International Task Force [5]**.** The new definitions provide some important adjustments that aim to clarify, simplify, and provide greater consistency.

The old concept that sepsis simply constitutes a systemic inflammatory response syndrome to infection is outdated. Sepsis represents a dysregulated host response that is far more complex than just ‘inflammation’ alone. Rather, sepsis comprises dysfunction of multiple pathways including anti-inflammatory, neural, hormonal, metabolic, bioenergetic, coagulation, and macro- and microvascular. Indeed, many of the SIRS criteria (temperature, heart rate, respiratory rate, white count) may simply reflect an appropriate host response to infection. SIRS thus fails to clearly differentiate an uncomplicated infection that may/may not need antibiotics from the more severe, life-threatening condition caused predominantly by an excessive and inappropriate host response driving the development of organ dysfunction [4]. Thus, old ‘*severe sepsis’* becomes the new ‘*sepsis’*.

The new sepsis definitions are accompanied by specific clinical criteria that offer greater consistency. Crucially, these criteria have been informed by analysis of multiple large electronic healthcare record databases totalling approximately a million patient episodes of presumed infection [10,11].

In the original 1992 definitions ‘organ dysfunction’ and ‘septic shock’ were too loosely defined. As a result, severe sepsis and septic shock were characterized in multiple ways, leading to marked variation in incidence and mortality [10]. To achieve uniformity, organ dysfunction is now described by a rise in

Sepsis-related Organ Failure Assessment (SOFA) score ≥2 points related to the infection episode, as this is associated with a 10% increase in mortality risk [11]. A change in SOFA is required as many patients have other acute or chronic comorbidities that yield independent SOFA points not related to sepsis. While SOFA has its limitations, particularly the key cardiovascular domain, it is the most familiar organ dysfunction scoring system in current use and a rising score correlates well with mortality risk [12]. However, two sequential measurements of SOFA are not mandated because patients with chronic comorbidities often have known baseline levels of indices, particularly renal (creatinine) and hepatic (bilirubin). Similar hospitalized patients, many of whom develop nosocomial sepsis, may have baseline levels taken on hospital admission or at a preoperative assessment clinic. In the absence of any prior history, it is assumed that, in most cases, the SOFA score will be zero prior to the onset of infection.

The new definition of septic shock identifies an infected patient with a combination of cardiovascular and cellular/metabolic abnormalities that would place them at a much higher risk of death compared to having either abnormality alone. For operationalization and consistency, septic shock is denoted by both hypotension and hyperlactataemia persisting after adequate volume resuscitation (Table 1).

Clearly, defining sepsis and septic shock, and developing clinical criteria to identify such patients, is an ongoing iterative process that will further evolve as new insights and novel diagnostics emerge.

Microorganisms and biomarkers

Biomarkers such as C-reactive protein (CRP), white blood cell count, lactate and procalcitonin (PCT) have classically been used to assist in the diagnosis and prognostication in patients with sepsis. Alas these biomarkers only offer a moderate diagnostic performance [13] and predictive abilities that do not differ greatly from readily available clinical scoring systems [14]. This has prompted intensive care physicians and researchers to re-think the everyday use and future visions for biomarkers in sepsis.

New developments in microbiology and biomarkers may shorten the time to diagnosis of the underlining microorganism and identification of its antimicrobial resistance pattern. This should optimize the treatment of infection in critically ill patients [15]. Such developments include various molecular techniques using nucleic acid testing (NAT) based on pathogen lysis, nucleic acid extraction and purification, amplification of nucleic acids by polymerase chain reaction (PCR) and identification by various methods, such as ELISA-based hybridization, fluorescence based real-time detection, liquid or solid phase microarray detection, sequencing and database recognition [16]. A well-described method is Matrix assisted laser desorption / ionization time-of-flight (MALDI-TOF) mass spectrometry (MS). This enables identification of isolated colonies of bacteria and fungi from culture in less than one hour utilizing an easily implemented, highly accurate, inexpensive and rapid technology [17]. The recently launched IRIDICA system, utilizing polymerase chain reaction/electrospray ionization (PCR/ESI) mass spectrometry now offers identification of up to 800 pathogens within 6 hours of blood sampling without the need to wait for culture positivity [18].

The detection of urinary antigens of *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1 in patients with pneumonia has been used broadly over the last decade. Single or multiple (multiplex) panels for the detection of a wide range of respiratory, gastrointestinal and central nervous system pathogens (bacteria, fungal, viral and *Mycobacterium tuberculosis*) have recently been

developed. Examples include the BioMérieux Biofire system that may identify pathogens on a wide variety of specimens including respiratory secretions, blood and stool and can identify up to 20 different pathogens [19] and the Xpert MRSA/SA skin and soft tissue infection assay (GeneXpert, Cepheid® Inc., Sunnyvale, CA, USA), which is approved for rapid detection (within 1 h) of MRSA and MSSA in wounds. When directly applied to synovial fluid and tissue specimens (e.g., bone, muscle, fascia, etc.) it also shows promise for the early diagnosis of osteoarticular and chronic prosthetic joint infections due to *Staphylococci* [20].

In some cases the panels for the early diagnosis of *Mycobacterium tuberculosis* are accompanied by the identification of resistance genes [21–23]. With regard to fungal infections, diagnostics include the pan-fungal assay (Fungitell®) test detecting the fungal cell wall component (1 →3)-β-D-glucan as well as the platelia enzyme immunoassay (GM-EIA) method that can detect *Aspergillus* galactomannan in serum and bronchoalveolar lavage fluid [24]. A monoclonal antibody (MAb)-based assay detects *Aspergillus*-specific MAb (JF5) using hybridoma technology and an immuno-chromatographic lateral-flow device as a point-of-care test. An advantage of this method may be detection of *Aspergillus* activity since MAb JF5 binds to an extracellular glycoprotein antigen secreted during the active growth of the fungus [24].

Several biomarker-guided antibiotic treatment strategy trials in sepsis have been published over the last years, most based upon PCT. In the PRORATA trial (n=621), a PCT-guided treatment strategy decreased the duration of an antibiotic course among intensive care patients with suspected bacterial infection [25]. A firm conclusion could not be reached, however, due to insufficient power for clinically relevant differences in mortality and low adherence to the treatment algorithm. A recent larger trial testing basically the same hypothesis, confirmed a reduction in antibiotic use and no apparent harm from this strategy [26]. In another trial, 1,200 intensive care patients were randomized to usual care vs. a PCT-directed algorithm whereby antibiotic therapy was intensified whenever the biomarker level increased [27]. However, the PCT-based strategy failed to improve outcome overall nor in any subgroups as compared to usual care, while duration of antibiotic use, mechanical ventilation and ICU stay were all lengthened. A strategy of antibiotic escalation based on PCT results should be discouraged.

Targets for future biomarker research and use in sepsis include:

i) Increasing the availability of novel biomarkers of core pathophysiological processes - not just biomarkers of undifferentiated organ dysfunction or pathogen presence. In this way, patients can be identified for personalized interventions targeted towards host-specific pathophysiology

ii) Transcriptomic (gene-activity) analysis that will enable a differentiated patient-specific knowledge of host-response mechanisms. Gene expression signatures (activation or suppression) are being developed for clinical use [28,29]

iii) Metabolomic and proteomic analysis in selected patients to further substantiate the immunological and metabolic host-response processes driving the key pathophysiology of sepsis and its complications [30]

iv) Conducting trials powered for clinically relevant differences and patient-important outcomes using biomarker-guided inclusion and intervention. Candidate surveillance molecules that can differentiate the pathophysiological processes in sepsis patients may serve as biomarkers for personalized interventions. These include soluble thrombomodulin (profound endothelial damage)

[31], surfactant protein D (alveolar lung damage) [32] and gelsolin (capability of host to respond adequately to actin release) [33]. By contrast, continuing the quest for the *magic bullet biomarker for sepsis diagnosis* may prove fruitless

v) Implementing point-of-care biomarker tests especially when standard laboratory test results cannot be obtained in a timely manner

Taken together, correct and rapid therapeutic decisions in patients with sepsis depend on skilled intensivists using tools such as modern microbiological methods and novel biomarker-guided treatment strategies that have been validated in appropriately powered randomized trials.

Antibiotics

Current clinical standard of practice for bacterial identification is age-old technology, with often a 48 hour plus delay. MALDI-TOF and PCR/ESI mass spectrometry systems shorten this wait, with even newer technology on the horizon for point-of-care PCR to identify bacteria at the bedside, as described above. Currently, 'best-guess' empiric therapy is commenced to cover the likely pathogens, including resistance patterns, and switching or de-escalating once identification and sensitivities have been obtained.

The use of broad-spectrum antibiotics causes collateral damage, including overgrowth of potentially pathogenic bowel flora. The gut microbiome can change within days [34]. Antibiotic administration may cause bacteria in the bowel and other sites to become resistant. The balance between benefit and harm of any antibiotic administration should always be considered. Long courses of antibiotics often have no benefit and can predispose to overgrowth of resistant flora over normal resident commensal flora [35].

The syndromes for which we use antibiotics are insensitive and non-specific. This is especially applicable to ventilator-associated pneumonia (VAP) [36] but also occurs in other patient populations where infection is difficult to differentiate from non-infectious inflammation, such as immunosuppressed patients and those with ventriculitis, burn injury and pancreatitis.

While PCT may be helpful in limiting the duration of antibiotic therapy, we need a better biomarker of infection in the presence of the ubiquitous inflammatory response [29]. While there may be scepticism regarding identification of an ideal biomarker for infection (see above), this would allow antibiotic sparing.

There are no new classes of antibiotics in the immediate drug pipeline. There are variations on current classes with new betalactam-betalactamases (ceftalozane-tazobactam, ceftazime-avibactam, ceftaroline-avibactam) and a new aminoglycoside (plazomicin). Importantly, novel monoclonal antibody, peptide and phage therapies are being investigated but these are at least a decade away from commercialization. We therefore have to use what is currently available but in a rational and cautious manner. Inhaled antibiotics for pulmonary infections seems a logical approach and is being used in some countries but exactly how, when, how much and for how long still needs to be refined [37].

Therapeutic drug monitoring (TDM) for toxicity of aminoglycosides and glycopeptides has allowed the development of easy-to-use immunoassays. While still rare to use TDM for beta-lactam antibiotic dosing [38], critically ill patients often need differing doses to the standard dose approved at drug registration. With increasing requests for beta-lactam measurements, TDM assays will become more commonly used. This need is becoming more important as antibiotic under-dosing may allow bacterial regrowth and predominance of resistant organisms [39].

Resuscitation triggers and targets

Historically, the evaluation of the relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2) was popular with attempts to place the patient on the independent part of the DO_2 relationship [40]. However this approach has been abandoned due to the complexity of the measurements and the inability to find oxygen delivery-dependent oxygen consumption when using non-coupled measurements [41]. An alternative approach of maximizing oxygen delivery was proposed, but this often led to treating septic patients with excessive amounts of fluids and inotropic agents and was thus also abandoned.

The current goals of resuscitation mostly focus on mean arterial pressure, central venous O_2 saturation ($ScvO_2$) and lactate as surrogates of adequate organ perfusion. A mean arterial pressure target is used as an indicator of tissue perfusion pressure. Maintenance of an adequate arterial pressure is important for organ blood flow distribution; some organs such as the splanchnic organs are very sensitive to reductions in arterial pressure. The optimal pressure target is still an issue of intense debate [42], but it seems that individualized therapy based on preexisting hypertension and response to therapy may be more valuable than standardized blood pressure targets. Even though challenged [43], $ScvO_2$ may remain a target in the early resuscitation of patients with a severely impaired circulation. The recent Early Goal-Directed Therapy trials enrolled overall less sick cohorts of patients (e.g. most had normal $ScvO_2$ values at inclusion and 20% were not admitted to an ICU and observed mortality rates were therefore low). Arguably, it may be that more severely ill patients with low baseline $ScvO_2$ may benefit from early resuscitation strategies guided by $ScvO_2$ [44]. Similarly, increased lactate levels are associated with a poor outcome and often trigger resuscitation efforts. A rapid lactate decrease (sometimes wrongly called lactate clearance) may also be a therapeutic target. This target may be difficult to use and interpret because increased lactate levels can be of non-hypoxic origin and lactate clearance can be decreased in liver disease.

Veno-arterial PCO_2 gradients are attractive indicators of tissue perfusion and may even be a future resuscitation target. The difference between central venous and arterial PCO_2 ($PvaCO_2$), reflects flow stagnation. When $ScvO_2$ is abnormal, $PvaCO_2$ mostly reflects a low cardiac output. However, when $ScvO_2$ is above 70%, then $PvaCO_2$ may reflect microcirculatory perfusion [45]. In patients with septic shock, $PvaCO_2$ values >6 mmHg were associated with poor outcomes in patients who had normalized their $ScvO_2$ [46]. Changes in $PvaCO_2$ in the first 6 hours of ICU admission may also be informative; patients with an initial $PvaCO_2$ >6 mmHg that normalized with treatment had lower mortality [47]. These observations need confirmation in large multicenter cohorts.

It may be that the same blood samples can be used to estimate respiratory quotient. Respiratory quotient is computed as CO_2 production divided by oxygen consumption. According to the Fick equation this ratio can be computed as cardiac output x CO_2 content difference / cardiac output x arteriovenous O_2 difference. Hence, this can be simplified into CO_2 content difference / arteriovenous O_2 difference. This ratio may not only predict the occurrence of VO_2/DO_2 dependency [48] but may also associated with a poor outcome. If so, it may be used to differentiate hyperlactatemia of hypoxic and non-hypoxic origin, but this is still controversial. A tentative clinical decision algorithm based on veno-arterial PCO_2 differences is presented in Figure 1.

Finally, the microcirculation may also be an important therapeutic target. Microcirculatory alterations are often present in patients with sepsis [49] and are associated with organ dysfunction and a poor outcome [50]. At this stage, even though attractive, using the microcirculation as a resuscitation target is premature. Even though current technology allows bedside assessment, the level of microvascular perfusion that should be targeted remains uncertain. More importantly, which agents that should be used to improve the microcirculation require identification.

Fluids

While fluid resuscitation has an established role in the early treatment of sepsis, there is evidence that both the type of fluid used and the cumulative dose administered over the course of the ICU admission may independently affect patient-centred outcomes. There is increasing recognition that resuscitation fluids must be used with the same caution and care as any other potentially toxic intravenous drug.

Following the publication of pivotal randomised clinical trials (RCTs) [51, 52] and updated systematic reviews [53], there is compelling evidence that hydroxyethyl starch (HES) solutions are associated with increased use of renal replacement therapy and increased mortality in patients with severe sepsis. Accordingly, medical regulatory authorities and clinical practice guidelines [54] recommend against the use of HES in these patients. Recent international cross-sectional studies have confirmed significant reductions in HES usage in critically ill patients [55].

While there is little evidence to support the use of colloids over crystalloids in sepsis, there are some data to suggest that albumin, used both as a resuscitation fluid [56], or to maintain a serum albumin above 30 g/L [57], may be associated with improved outcome. These results have to be confirmed as they were obtained in secondary analyses. The pooled estimates in a recently updated meta-analysis did not show improved survival with albumin versus crystalloids in patients with sepsis [58].

There is also some evidence, primarily from observational studies, that 0.9% sodium chloride (saline) is associated with the development of a hyperchloraemic metabolic acidosis, particularly when administered in higher doses; this may result in the development of acute kidney injury (AKI) and increased mortality in critically ill patients, compared to low-chloride containing crystalloids [59]. However, a recent cluster cross-over RCT did not demonstrate differences in the rates of AKI nor mortality in ICU patients who received either a buffered salt solution or saline, although the power of this trial was limited because of a low number of clusters [60]. Several large-scale RCTs comparing these crystalloids in high-risk ICU patients are underway to address this key question regarding the choice of crystalloid for resuscitation in sepsis.

The development of a net positive fluid balance due to the over-administration of fluid is associated with adverse outcomes in patients with sepsis [61]. Strategies to use more restrictive fluid resuscitation methods during the early phase of management, and subsequent strategies to remove excess fluid or 'de-resuscitate' patients during the later phases of recovery, are advocated. However, these have not been evaluated in specific process-of-care RCTs in patients with sepsis. There is an imperative to conduct these trials and to amend practice guidelines that recommend relatively large volumes of resuscitation fluids (e.g. at least 30 mL/kg) [62].

Vasopressors

Norepinephrine is the current recommended first line vasopressor in septic shock, to which vasopressin may be added [62]. As new vasopressors are developed, there will be new approaches for patients with septic shock but also novel questions. Increased vascular leak and endothelial permeability are common in septic shock. At least one new vasopressor (selepressin) decreased indirect markers of vascular leak in pre-clinical studies [63] and a Phase II RCT (NCT01000649).

Vasopressors can produce untoward effects, including organ dysfunction. Increased use of catecholamine vasopressors has been associated with an increased rate of atrial fibrillation [42] which, in turn, is associated with an increased risk of stroke in patients with sepsis [64]; mitigating this risk may also be important. Monitoring vasopressor selection and dose will be complemented by more non-invasive cardiovascular assessment (e.g. non-invasive cardiac output, microcirculation) to limit vasopressor exposure and allow earlier de-resuscitation. One RCT found that corticosteroids significantly decreased the duration of vasopressor use compared to placebo, but did not decrease short-term mortality [65]. As the mortality of septic shock has decreased [Gaieski DF, Edwards JM, Kallan MJ, Carr BG (2013) Crit Care Med 41:1167–1174. doi: 10.1097/CCM.0b013e31827c09f8], RCTs of vasopressors now focus on improving short-term outcomes (such as days alive and free of vasopressors with maximum penalty for death (for example NCT02508649). Such approaches may eventually be linked to improved long-term outcomes [67].

Future vasopressors will have additional potentially beneficial, non-vasoconstricting properties (Table 2). Selepressin is a potent, selective vasopressin V1a agonist that is now in a Phase IIB/III pivotal multicentre RCT in septic shock. Angiotensin-II decreased norepinephrine requirements in septic shock [68] and is now being investigated in a larger multicentre RCT. Methylene blue [69], a cyclic GMP blocker, is a potent vasopressor in septic shock that may decrease pulmonary vascular leak [70] and deserves evaluation in larger RCTs.

A DDAH1 (dimethylarginine dimethylaminohydrolase) selective inhibitor (L-257) may also have promise in septic shock [71]. DDAH1 is an enzyme that metabolizes endogenously produced nitric oxide synthase inhibitors, principally ADMA (asymmetric dimethylarginine). L-257 increased ADMA concentrations, decreased norepinephrine requirements and prolonged survival in two rodent models of septic shock [71].

A major frontier for vasopressors in septic shock is use of predictive biomarkers (i.e. pharmacogenomics) to enrich trial inclusion and ultimately to increase efficacy and safety of vasopessors [72]. Pharmacogenomics are applicable to norepinephrine [73], epinephrine, vasopressin

[74] and corticosteroids [75, 76] that could better decrease vasopressor dose, duration and adverse effects. Predictive biomarkers could also enrich signal for vasopressors in development such as the V1a agonist selepressin (plasma angiopoietin-2 because selepressin decreases plasma angiopoietin-2, a mediator of increased permeability and the leucyl/cystinyl aminopeptidase (LNPEP) genotype, which has been associated with altered vasopressin clearance and activity [74]) and angiotensin-II (such as variants of angiotensin II type 1 receptor-associated protein [77]). Protein biomarkers (such as cytokines) are also under-evaluated and could also enrish response to vasopresors and corticosteroids [76].

A predictive biomarker (also known as a companion diagnostic) uses genomics to define enhanced efficacy or increased safety with a drug (www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407297.htm) . At present about 100 drugs have approved predictive biomarkers (www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm).
Predictive biomarkers could be applied to enhance drug efficacy and safety in sepsis; genomic variants intersect with the corticosteroid and vasopressin axes for prediction of response to steroids (and less so vasopressin), in part because steroid and vasopressin genomic variants are well described in many non-septic conditions. Predictive biomarker discovery often follows a candidate gene approach, utilizing knowledge of drug receptors, transporters, enzymes that metabolize a drug and drug target pathways. Predictive biomarkers can also enhance drug development. Pharmacogenomics (PGx) could increase chances of drug development success in sepsis by enriching the heterogeneous population. Variants of PCSK9 were associated with outcomes of sepsis and post-treatment of cecal ligation and perforation model mice with PCSK9 inhibitors decreased inflammation, cardiovascular dysfunction and mortality; thus, PCSK9 inhibition could be an effective target in sepsis (Walley KR, Thain KR, Russell JA, et al. *Sci Transl Med* 2014, **6**(258):258ra1). Potential predictive biomarkers/companion diagnostics could be also used with recombinant human thrombomodulin, selepressin, angiotensin II, PCSK9 inhibitor, and esmolol.

Just as in cancer therapuetics today, another frontier we see is the use of more rational combinations of vasopressors each in lower doses and given according to specifc patient vasopressor pathway deficits such as vasopressin for vasopressin definciency, angiotensin II for ACE deficiency in ADRDS complicated by septic shock, and even use of short-acting beta-blockers such as esmolol [78] in patients who are over-sensitzed to and have excessive adrenergic responses. As an example of vasopressor combinations, a very recent study showed that vasopressin was used in numerous vasopressor combinations in septic shock, but it is unclear how clinicians chose these various vasopressor combinations (Russell, J., personal communication). Genomic and other biomarkers could assist in more rational selection of the vasopressor combinations.

Inotropes

Despite the three recent multicentre studies showing that protocolised early goal-directed therapy, aiming to achieve specific haemodynamic and haemoglobin targets, does not need to be used routinely for all patients with septic shock [43], maintaining an adequate cardiac output is still an important part of septic shock management.

Myocardial dysfunction is common in sepsis. Detailed echocardiographic examination reveals that myocardial dysfunction can be present even in the absence of a drop in cardiac output or ejection fraction [79]. Even if depressed cardiac function is absent at first presentation, myocardial dysfunction frequently develops over the first 24 hours. To fully understand the pathophysiological processes leading to hypotension and hypoperfusion in an individual with sepsis, detailed echocardiography may be required. However, it will be challenging to train all intensivists to perform echocardiography in a technically-difficult patient population [80]. Even if only trained to a limited level of practice, they will still then require ongoing support to maintain these competencies. Data are needed from high-quality trials assessing if the use of echocardiography improves care and outcomes.

It remains uncertain what to do when myocardial dysfunction is present. The dangers of using high dose dobutamine to increase cardiac output have been known for two decades [81]. The hazards of excessive catecholamine stimulation through tachycardia, arrhythmias, myocardial injury and direct toxic effects, are all well described [82]. An interesting alternative to catecholamines is levosimendan, which has a unique set of actions that make it an attractive possibility for use in sepsis. It sensitises the myocardium to calcium by binding to troponin C, increasing myocardial contractility without increasing oxygen demand, and it opens vascular smooth muscle potassium channels leading to vasodilation. It also appears to protect the myocardium from ischaemic insult and to have anti-inflammatory properties [83]. Meta-analyses of trials of critically ill patients in general and small trials in sepsis suggest levosimendan may improve outcomes [84, 85], but the results of larger ongoing trials (ISRCTN12776039) are awaited before its role in sepsis is clear [86].

An alternative approach may be to simply limit catecholamine use or even consider beta-blockers for patients who remain tachycardic and on high dose catecholamines. The results of a single-centre trial demonstrating reduced mortality (a secondary outcome) with esmolol treatment in this patient population are intriguing [78], but beta blockers should not yet be used as part of routine clinical care. The intensive care community has learnt that caution should be exercised before widely adopting treatment strategies from single centre, unblinded studies with a high control group mortality and a large treatment effect [87]. Larger multi-centre trials are required to validate these findings, as well as to explore the mechanism of action of beta-blockers. Are they acting simply to reduce heart rate and thus potentially improve cardiac performance or do they have other non-cardiac effects? Of note, esmolol altered transcription of immune genes in an animal model of septic shock [88], suggesting that its mechanism of action could be more than simply decreasing heart rate. The interaction between beta-blockers and novel vasopressors/inotropes (e.g. selepressin, angiotensin-II, levosimendan) should also be explored.

Blood

Sepsis and other inflammatory illnesses result in anaemia through multiple mechanisms. Haemorrhage and blood sampling contribute, but impaired erythropoiesis is important especially in “chronic” critical illness and during recovery. Iron deficiency, whether absolute or functional, may contribute and replacement seems logical. Hepcidin, which blocks intestinal iron uptake and promotes iron sequestration into macrophages, is up-regulated in inflammatory conditions [89]. However, a recent trial in trauma patients found no benefit from intravenous iron therapy [90], while current

evidence does not support its use during critical illness. The ongoing IRONMAN trial (ACTRN12612001249842) may provide answers, at least for anaemic general ICU populations. The risk-to-benefit profile of intravenous iron therapy during sepsis requires future study, because potential benefits from increasing erythropoiesis may be offset by increased infections associated with iron therapy. Hepcidin measurement is a potential indicator of true iron deficiency during critical illness that could provide a precision medicine approach to therapy, and future trials should explore its use as a potential biomarker to guide therapy. There are also ongoing trials of hepcidin antagonists in chronic anaemia, and these may merit investigation during critical illness.

Blood transfusion remains the most effective treatment for anaemia during critical illness, but risks from allogeneic blood remain a concern. Recent data are reassuring. A meta-analysis of RCTs found no increased infection risk with liberal transfusion, even when restricted to trials in critical care patients [91]. Despite the biological plausibility of an important red cell storage lesion effect, the ABLE [92] and RECESS [93] trials found no benefit from exclusive use of fresher blood in critical care (including sepsis) and cardiac surgery populations, respectively. These RCTs contradict observational studies, and suggest that currently supplied blood product is inherently safe. Recent systematic reviews indicate the safety of restrictive transfusion triggers for most patients, including the critically ill [94]. Most high quality RCTs used a haemoglobin trigger of 70 g/L, but uncertainty remains when to use higher thresholds. Recent RCTs however provide some clues. A recent trial in patient with septic shock [95] found no difference in outcomes between a haemoglobin trigger of 70 g/L versus 90 g/L, including the need for organ support and the rate of ischaemic events. This trial is consistent with the lack of effect seen in the protocolised early goal directed therapy trials [43], suggesting that using red cells to increase oxygen delivery is not effective in sepsis. A possible exception may be early septic shock with clear evidence of inadequate oxygen delivery (low central venous O_2 saturation ($ScvO_2$)) a finding that was relatively rare in the three recent EGDT trials [43]. The planned individual patient data meta-analysis of the three trials may provide answers.

Uncertainty still remains for the patient with concurrent cardiovascular disease because these were excluded in many trials. Few data are specific to sepsis, although there is physiological plausibility for a greater risk of myocardial injury from coronary supply-demand imbalance particularly in septic shock where tachycardia and diastolic hypotension may compromise coronary blood flow. A recent systematic review of RCTs involving patients with chronic cardiovascular disease, which included several critical care trials, also suggested a higher rate of acute coronary syndrome with restrictive practice [98]. Clearly uncertainty remains whether a haemoglobin trigger of 70 g/L is safest for septic patients with concurrent ischemic heart disease. Such patients have been underrepresented in most critical care trials and are at high risk. The National Institute for Health and Care Excellence (www.nice.org.uk/) guidance for blood transfusion makes future research in this area a key research recommendation for the future.

Perspectives

The process of care and treatment of patients with sepsis has been vastly improved over the last few decades through extensive clinical, investigational and organisational focus. In many therapeutic and diagnostic areas there are still work ongoing to facilitate further improvements over the next few years (Table 3). Collaborative educational and research initiatives by scientific societies and academic groups, and global organisational initiatives including the Surviving Sepsis Campaign, the Global Sepsis

Alliance and the World Sepsis Day have all played major roles and should continue to do so. These initiatives are run by dedicated colleagues from our community. We can all contribute by taking an active part in these organisations or their activities as national, regional or local champions or investigators. Together we offer a huge potential; however, it is up to us as individuals in the critical care community to make the difference as it is highly unlikely that others will do it for us. Collaborative efforts are very much needed if improvements are to continue to be made and to become truly global, so that patients with sepsis in all corners of the world may benefit from the care improvements obtained to date and from those to come.

Conflicts of Interest

AP is member of the steering committee and national investigator of a vasopressin trial in septic shock sponsored by Ferring Pharmaceuticals; his department is reimbursed for his time. The department also receives research funding from Fresenius Kabi and CSL Behring.

ACG has received speaker fees from Orion Pharmaceuticals. He has consulted for Ferring Pharmaceuticals, Tenax Therapeutics and received grant support from Orion Pharmaceuticals, Tenax Therapeutics and HCA International with funds paid to his institution. He is the Chief Investigator for two NIHR funded trials in septic shock, VANISH – examining vasopressin and LeoPARDS – examining levosimendan.

DDB is member of the steering committee of Surviving Sepsis Campaign. He was PI of the SOAP II study that compared dopamine and norepinephrine for the treatment of shock. He is member or contributed to the advisory board of Nestlé and Baxter, received honoraria for lectures from Griffols, Edwards Lifesciences and Nihon Kohden, and grant or material for research from Edwards Lifesciences, Pulsion, LiDCO, Vytech, Cheetah Medical, Nexfin, and Imacor, none of these being relevant to the content of this article.

GD is a member of advisory boards on severe infections for ASTELLAS, PFIZER, BAYER and MERCK, he has received honorarium fees for lecture tours from ASTELLAS, PFIZER, MERCK, BAXTER, GILEAD while his department is one of the 3 main partners of EU/FP7 project named "MAGIC BULLET".

JM's institution, the George Institute for Global Health, Sydney has received logistical support, unrestricted grant and reimbursement for travel expenses from Fresenius Kabi in relation to the conduct of the Crystalloid vs. Hydroxyethyl Starch Trial; unrestricted grant and reimbursement for travel expenses and participation on Advisory Board from Baxter Health in relation to fluid resuscitation research; unrestricted grant from CSL Bioplasma in relation to fluid resuscitation research. He has received no direct personal remuneration.

JR reports patents owned by the University of British Columbia (UBC) that are related to PCSK9 inhibitor (s) and sepsis and related to the use of vasopressin in septic shock. JR is an inventor on these patents. JR is a founder, Director and shareholder in Cyon Therapeutics Inc. (developing a sepsis therapy). Dr. Russell has share options in Leading Biosciences Inc. JR is a shareholder in Molecular You Corp. JR reports receiving consulting fees from Cubist Pharmaceuticals (now owned by Merck; formerly was Trius Pharmaceuticals; developing antibiotics), Ferring Pharmaceuticals (manufactures

vasopressin and is developing selepressin), Grifols (sells albumin), La Jolla Pharmaceuticals (developing angiotensin II; JR chairs the DSMB of a trial of angiotensin II), CytoVale Inc. (developing a sepsis diagnostic), and Asahi Kesai Pharmaceuticals of America (AKPA)(developing recombinant thrombomodulin). JR reports having received grant support from Ferring Pharmaceuticals that was provided to and administered by UBC.

MS is a co-investigator of the UK Department of Health-funded LeoPARDs trial examining the role of levosimendan in septic shock, and Clinical PI of a large multicentre sepsis biomarker study conducted by the UK Ministry of Defence (DSTL). He is Co-PI of a sub-study of the EU Innovative Medicines Initiative Combacte-Magnet Program. He sits on advisory boards for Biotest assessing the role of immunoglobulins in septic shock, and Bayer's novel amikacin nebuliser therapy for hospital-acquired pneumonia. He chairs the Data Monitoring Committee for InflaRx's Phase II trial of a novel C5a inhibitor. He is also developing a novel tissue oxygen sensor supported by the Wellcome Trust and UK Department of Health that is shortly to undergo clinical trials.

TSW has received consultancy fees to his institution (Edinburgh University) over the past 5 years from GE Healthcare and Selex; neither were relevant to the content of this article.

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99. NICE guidelines [NG24] - Blood transfusion.

Table 1. New sepsis terms and definitions

- **Sepsis** is defined as life-threatening organ dysfunction due to a dysregulated host response to infection
- **Organ dysfunction** can be identified as an acute change in total SOFA score ≥2 points consequent to the infection. The baseline SOFA score can be assumed to be zero in patients not known to have pre-existing organ dysfunction.
- **Septic shock** is a subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
- **Patients with septic shock** can be identified using a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg, AND a blood lactate >2 mmol/l persisting after adequate fluid resuscitation
- **qSOFA** ('quickSOFA') is a rapid bedside screen to identify community, emergency department and ward patients at risk of having sepsis (as confirmed by subsequently measuring a change in SOFA ≥2). Patients with suspected infection having two or more of: systolic BP ≤100 mmHg, altered mentation and/or respiratory rate ≥22 breaths/min have a significantly increased risk of dying compared to those with 0 or 1 qSOFA criteria measured around the time cultures are taken and antibiotics commenced
- **N.B. Systemic Inflammatory Response Syndrome – SIRS -** and **severe sepsis** are now redundant for the diagnosis of sepsis and sepsis-related organ dysfunction.

SOFA: severity organ failure assessment; MAP: mean arterial pressure.

Table 2. Novel vasopressors, their additional potential benefits, current trial development status and relevant biomarkers

Drug	Receptor Activity/ Mechanism of Vasoconstriction	Possible Additional Beneficial Actions	Trial Development Phase	Possible Relevant Biomarkers
Selepressin	V1a agonist	↓ Ang-2 ↓ vascular leak	IIB/III	LNPEP Ang-2 Vasopressin/copeptin
Angiotensin-II	Angiotensin II receptor agonist	↑ vasopressin ↑ erythropoietin	III	AGTRAP
Methylene blue	cGMP antagonist	↓ vascular leak	NA	
L-257	Selective inhibitor of DDAH1	↓Norepinephrine dose	Pre-clinical	Expired NO metabolites Plasma nitrite/nitrate

AGTRAP: angiotensin type II receptor-associated protein; Ang-2: angiopoietin-2; DDAH1: dimethylarginine dimethylaminohydrolase; LNPEP: Leucyl/cystinyl aminopeptidase is also known as vasopressinase; cGMP: cyclic GMP.

Table 3. Selected processes for imminent improvements in sepsis care

Therapeutic or diagnostic area	**Process**
Definitions	Continued iterative process, which should challenge and modify the definitions
Microorganisms and biomarkers	Testing of *omics* driven diagnostic and stratification of patients
Antibiotics	Therapeutic drug monitoring for more and more antibiotics
Haemodynamic triggers and targets	Testing of protocols driven by $PvaCO_2$ and markers of microcirculatory impairment
Fluids	Testing of different volumes of fluids and different crystalloid solutions
Vasopressors and inotropes	Development and testing of non-catecholamines
Blood	Testing different transfusion strategies in subgroups of high risk Testing iron supplementation

Figure legends

Fig. 1. A tentative algorithm of veno-arterial differences in CO_2 ($PvaCO_2$) based on physiological interpretation of human and experimental studies. In the model central venous O_2 saturation ($ScvO_2$) is assessed as a marker of low cardiac output.