Sepsis and septic shock

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Sepsis is a common condition that is associated with unacceptably high mortality and, for many of those who survive, long-term morbidity. Increased awareness of the condition resulting from ongoing campaigns and the evidence arising from research in the past 10 years have increased understanding of this problem among clinicians and lay people, and have led to improved outcomes. The World Health Assembly and WHO made sepsis a global health priority in 2017 and have adopted a resolution to improve the prevention, diagnosis, and management of sepsis. In 2016, a new definition of sepsis (Sepsis-3) was developed. Sepsis is now defined as infection with organ dysfunction. This definition codifies organ dysfunction using the Sequential Organ Failure Assessment score. Ongoing research aims to improve definition of patient populations to allow for individualised management strategies matched to a patient's molecular and biochemical profile. The search continues for improved diagnostic techniques that can facilitate this aim, and for a pharmacological agent that can improve outcomes by modifying the disease process. While waiting for this goal to be achieved, improved basic care driven by education and quality-improvement programmes offers the best hope of increasing favourable outcomes.

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Introduction

Sepsis is a complex disorder that develops as a dysregulated host response to an infection, and is associated with acute organ dysfunction and a high risk of death. This syndrome needs urgent treatment, and thus awareness of the presenting characteristics is of great importance. The incidence of sepsis is high, and the condition remains one of the leading causes of death globally. Thus, sepsis is an important public health issue[1] with considerable economic consequences.[2] Over the past 30 years, a substantial amount of research and improved clinical processes have increased the speed of recognition and treatment of sepsis. In 2016, a new definition was developed to further refine this process, with an increased focus on recognising organ dysfunction in the context of infection.[3]

The World Health Assembly and WHO made sepsis a global health priority in 2017, and have adopted a resolution to improve the prevention, diagnosis, and management of sepsis.[4] In this Seminar, we summarise the most up-to-date evidence about sepsis. Although sepsis is a global priority, most of the available papers and evidence come disproportionately from high-income countries.

We acknowledge this limitation. More research and a greater understanding of sepsis is needed in every health-care system, particularly to better identify patient populations and personalise treatments. It is also important that the global research and quality-improvement agendas on sepsis do not neglect low-income and middle-income countries in the future. Three of the coauthors of this Seminar have been involved in the Surviving Sepsis Campaign (SSC), a global initiative aimed at improving survival in patients with sepsis and septic shock. Since its first publication in 2004, the SSC has established itself as the most important quality-improvement programme for sepsis globally, and the latest bundle was released in 2018. This Seminar presents up-to-date evidence and controversies about sepsis, and highlights the importance of driving quality improvement through initiatives such as the SSC.

Definition

In 2016, the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) defined sepsis as life-threatening organ dysfunction resulting from dysregulated host responses to infection,[3] and defined septic shock as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are profound enough to substantially increase the risk of mortality. The Sequential Organ Failure Assessment (SOFA) score is used to codify the degree of organ dysfunction (table).[5]

Based on the first observations described by Bone and colleagues in 1989[6] and following the 1992 consensus, sepsis was defined as the maladaptive systemic manifestation of an infection. Sepsis can arise because of many different infectious insults. The 1992 consensus panel proposed the term severe sepsis to refer to sepsis complicated by acute organ dysfunction, and the term septic shock for sepsis associated with hyperlactataemia or hypotension refractory to fluid resuscitation.[7]

There were several reasons for the creation of the new definition. First, the main limitations of the previous criteria, namely the poor specificity of many of the systemic inflammatory response syndrome (SIRS) criteria for sepsis, were already recognised in 2003.[8] To address these limitations, the new criteria for sepsis recognition focus more on codifying organ dysfunction than on identifying signs of inflammation.[3] In practice,

Search strategy and selection criteria

Two authors (MC and AR) independently searched MEDLINE, Embase, and Cochrane Database of Systematic Reviews using the keywords "sepsis" and "septic shock" and their related MeSH terms, with no language restrictions, for articles published up to April 2018. Review articles and guidelines, such as the Surviving Sepsis Campaign, were searched manually for additional references. The reference lists of the identified papers were also checked for additional articles.

	SOFA score 0	SOFA score 1	SOFA score 2	SOFA score 3	SOFA score 4
Respiratory system: PaO_2/FiO_2 (kPa)	≥53·3	<53·3	<40	<26·7	<13·3
Coagulation system: platelets (×10^3/μL)	≥150	<150	<100	<50	<20
Hepatic system: bilirubin (μmol/L)	<20	20–32	33–101	102–204	>204
Cardiovascular system	MAP >70 mm Hg	MAP <70 mm Hg	Dopamine <5 μg/kg per min, or dobutamine (any dose) administered	Dopamine 5·1–15 μg/kg per min, or epinephrine ≤0·1 μg/kg per min, or norepinephrine ≤0·1 μg/kg per min administered	Dopamine >15 μg/kg per min, or epinephrine >0·1 μg/kg per min, or norepinephrine >0·1 μg/kg per min administered
Central nervous system: Glasgow Coma Scale	15	13–14	10–12	6–9	<6
Renal system					
Creatinine (μmol/L)	<110	111–170	171–299	300–440	>440
Urine output (mL/day)	..	..	..	<500	<200

Scores from 0 to 4 are assigned for each of the six organ systems, with a higher score indicative of worse organ dysfunction in each system. MAP=mean arterial pressure.

Table: **Description of sequential organ failure assessment (SOFA) scoring system[5]**

although proinflammatory and anti-inflammatory processes are involved in the dysregulated response, sepsis is no longer considered to be only an inflammatory disorder. Second, the previous classification has been simplified, removing any reference to severe sepsis. In keeping with the common use of the terms, the previous categories of sepsis, severe sepsis, and septic shock have now been changed to infection, sepsis, and septic shock. Third, objective risk stratification tools have been used to define organ dysfunction. These tools are used to determine the SOFA score (table).[5] Thus, sepsis is now defined as the presence of an infection combined with an acute change in SOFA score of 2 points or more (with the baseline assumed to be 0 in patients without any known pre-existing organ dysfunction).

The 2016 panel further described three clinical criteria that can be used to identify hospital patients with infections who are likely to have either a prolonged stay in an intensive care unit (ICU) or who are at a high risk of death. These three criteria, identified from a retrospective analysis of large databases, were termed quick SOFA (qSOFA) variables, and patients are considered high risk if they meet at least two of the criteria, as follows: alteration in mental status, systolic blood pressure of less than 100 mm Hg, or a respiratory rate of more than 22 breaths per minute. This qSOFA score was found to be marginally superior to the original SIRS criteria in predicting this high-risk category of patients.[9,10] The qSOFA system is a simple risk stratification tool that can be used to identify patients at risk of sepsis. However, this system should not be used to rule out patients as being at high risk, as it is likely to be more specific, but not more sensitive, than the old SIRS criteria.[11] The new definitions still allow for clinical judgment for suspected sepsis.

Septic shock is described as a clinically defined subset of sepsis cases, wherein, despite adequate fluid resuscitation, patients have hypotension requiring vasopressors to maintain a mean arterial blood pressure above 65 mm Hg and have an elevated serum lactate concentration of more than 2 mmol/L.[3]

Incidence

The true incidence of sepsis in any given country is unknown. The reported incidence is dependent on the specific definition used, the infecting organism, the reporting mechanism (such as the use of the International Classification of Diseases-9 coding systems) and the requirement for either organ support or intensive care. These factors result in marked differences between estimates and discrete geographical locations. Most data describing the incidence of sepsis are from high-income countries, where 2·8 million deaths per year are attributable to sepsis.[12] In 2001, Angus and colleagues[13] reported that, in the USA, the incidence of severe sepsis was more than 750 000 cases per annum (300 cases per 100 000 population), equivalent to 2·26 cases per 100 hospital discharges. In the UK, the reported prevalence of sepsis in ICU-derived cohorts is 27% of all ICU admissions, whereas the prevalence is 12% in the USA.[14] This difference could partly be explained by the substantially greater numbers of ICU beds available in the USA than in the UK, and thus the differing triage patterns and admission criteria.[15,16] It is also possible that, in institutions where clinical staff are trained in sepsis recognition, the previous use of the less-specific SIRS criteria could have led to an over-reporting of sepsis cases.

Overall, however, there is probably a substantial under-reporting of the incidence of sepsis and with an ageing population, the incidence will continue to increase. This pattern might be further accentuated by campaigns to increase the awareness of and screening for the condition. Except for maternal and neonatal sepsis, the condition is usually considerably under-reported in the global burden of disease statistics. The true scale of the problem is probably much higher than what has been reported. Data suggest that sepsis contributes to between a third and a half of all in-hospital deaths in the USA.[17] Although these data represent the incidence of sepsis in high-resource countries, most deaths due to sepsis happen in low-resource countries, where the exact incidence of sepsis is difficult to accurately estimate. The available literature

suggests that an estimated 90% of worldwide deaths from chest infections occur in low-resource settings;[12] about 70% of the 9 million deaths due to chest infections in neonates and infants are associated with sepsis, and most cases occur in Asia and Africa.[18]

Sepsis can be a terminal event in patients who are already dying from other causes (eg, terminal cancer). This fact is especially important to remember in the context of an increased number of admissions of old and frail patients in hospital wards and ICUs,[19] and when evaluating our expectations on to what extent mortality rates from sepsis can be reduced. It is very likely that a baseline mortality from sepsis is part of the nature of the syndrome itself, and in practice it is unreasonable to expect mortality rates to drop to zero, despite our best efforts to understand, recognise, and treat the condition.

It is hoped that positive advancements, such as the recent World Health Assembly and WHO resolution on sepsis, will raise awareness of sepsis as a global priority, and its prevention, recognition, and treatment will improve worldwide.

Aetiology

Sepsis can originate from virtually any infecting organism. Therefore, the range of presentations of the syndrome is very wide and varies considerably between geographical regions.

Sepsis can originate from community locations or result from a stay in hospital or in another health-care facility. About 80% of hospital-treated sepsis cases arise in the community. The most common site of infection that leads to sepsis is the lung (64% of cases), followed by the abdomen (20%), bloodstream (15%), and renal and genitourinary tracts (14%).[20–22]

The Sepsis Occurrence in Acutely Ill Patients (SOAP) study reported an almost equal prevalence of Gram-positive and Gram-negative bacterial infections among patients with sepsis,[21] although Gram-positive bacterial infections might now be more common than Gram-negative,[23] with *Staphylococcus aureus* (Gram-positive) and *Pseudomonas* species and *Escherichia coli* (Gram-negative) being the most frequently identified organisms.[20,24] The 2012 Intensive Care Over Nations study, however, showed that Gram-negative bacterial infections were more common than Gram-positive bacterial infections in the USA.[24,25]

Pathophysiology

Sepsis is characterised by a systemic dysregulated host response to infection. One well-described pathway of immune activation in response to infection occurs when highly conserved microbial pathogen-associated molecular patterns are recognised by pattern-recognition receptors, including Toll-like receptors, on the cells of the innate immune system.[26] This interaction triggers the release of both proinflammatory and anti-inflammatory mediators through activation of nuclear factor κB and neutrophils.[27] Cytokines, such as tumour necrosis factor α, interleukin 1, interleukin 2, interleukin 6, interleukin 8, and others, cause neutrophil–endothelial cell adhesion, activate the complement and clotting cascades, and can lead to the generation of microthrombi.[27] Traditionally, sepsis was considered to be an overwhelming, systemic, proinflammatory response to infection that was followed by a phase of immunosuppression characterised by anergy, lymphopenia, and secondary infections.[27] Patients who survive early sepsis often develop nosocomial infections with organisms that are not typically pathogenic in immunocompetent hosts, and have reactivation of latent viruses. The programmed cell death protein 1 and interleukin 7 pathway has also emerged as an important mechanism underlying the inhibition of T-cell function, and is therefore associated with late sepsis and immunosuppression in patients who survive early sepsis. These observations led to the hypothesis that the early hyperinflammatory state evolves to a subsequent hypoinflammatory state with substantial immunosuppression.

Newer paradigms suggest that the proinflammatory and immunosuppression phases might occur simultaneously, with the intensity of both responses depending on multiple factors of both the host—such as genetics and comorbidities—and the pathogen—such as type, virulence, and burden.[27–29]

The precise mechanisms of cell injury and sepsis-induced organ dysfunction are not fully understood and continue to be an active area of scientific investigation. Sepsis commonly interferes with the distribution of systemic blood flow to organ systems via vasodilation and disturbances in microcirculation.[30]

Microscopic techniques based on orthogonal polarisation spectral imaging and sidestream dark-field imaging have allowed the acquisition of real-time images of the microcirculation. Image analysis for the quantification of microcirculatory dysfunction has traditionally been done offline, but new software packages are being developed for the purpose of quantifying dysfunction in real time.[31] Microcirculatory dysfunction has consistently been associated with worse outcomes.[32] Examples of preserved and altered microcirculation in patients with sepsis are shown in video 1 and video 2.

See Online for videos

Tissue ischaemia can occur because of either a systemic or local mismatch between oxygen delivery and tissue demand. Additionally, mitochondrial dysfunction can lead to a failure of tissue oxygen extraction despite sufficient oxygen delivery—termed cytopathic hypoxia.[33,34] Tissue hypoxia, mitochondrial dysfunction, and apoptosis are all thought to be important mediators of sepsis-induced organ dysfunction.[35] Organ dysfunction is an important predictor of patient outcome, with multiple organ dysfunction being associated with a high risk of death.[36]

Inflammatory mediators are also implicated in the coagulopathy often present in sepsis. Various coagulation

Panel 1: **Risk factors for infection and sepsis**

Risk factors for developing an infection

Generic infection

- Host genetics (eg, tumour necrosis factor α and Toll-like receptor polymorphisms)
- Extremes of age
- Genetic immunosuppression
- Exposure to epidemic
- Acquired immunosuppression or immune dysregulation (eg, cancer, immunosuppressive medications, diabetes, alcohol abuse, indwelling catheters, conditions with altered skin)

Primary bloodstream infection

- Indwelling catheters
- Parenteral nutrition

Chest infection

Same as for generic infection, plus

- Chronic obstructive pulmonary disease
- Prolonged intubation
- Recent thoracic, abdominal, major orthopaedic surgery
- Aspiration

Urinary tract infection

- Indwelling catheters
- Poor mobility (eg, in nursing home residents)
- Female sex

Risk factors for developing sepsis

- Less defined
- Same as for infection risk
- Host genetics

pathways are affected, and the manifestation, when present, can vary from massive thromboembolism to fibrin deposition in the microvascular bed. One severe complication is disseminated intravascular coagulation, which is characterised by microthrombosis and haemorrhage.[37]

Risk factors

Most of the described risk factors for the development of sepsis focus on a patient's predisposition to infection (panel 1). Very old or very young age, immunosuppressive diseases (eg, AIDS), cancer, immunosuppressive medications, diabetes, alcohol abuse, indwelling catheters, or other conditions involving altered skin integrity all predispose patients to infection.[21,36,38] There is also evidence that people who do not do adequate exercise have an increased risk of death if they develop sepsis.[39] Among patients with infections, the risk factors for the development of sepsis and organ dysfunction are less well characterised, but probably include comorbidities and host genetic factors in addition to pathogen-related factors (figure). Host genetics probably contribute to the risk of acquiring an infection as well as the risk of developing sepsis from an infection. Multiple studies have examined the influence of single-nucleotide polymorphisms in the development of infection and sepsis.[40–43] The most studied polymorphisms are those involving tumour necrosis factor α and Toll-like receptors. Because sepsis is a complex condition, multiple genes and gene–environment interactions are necessary for the development and clinical presentation of sepsis. Various candidate gene studies have identified polymorphisms, but these results have not yet been consistently replicated.[26] Although personalised therapy for sepsis based on an individual's genetic profile is not yet achievable, this area of investigation will continue to grow and individualised approaches to management are likely to be feasible in the future.

Clinical presentation

In sepsis, a host's response to an infection manifests as signs of infection together with acute organ dysfunction. This dysfunction can lead to multiple organ failure, acidosis, and death.[36] Although traditionally the SIRS criteria have been used to describe the onset of sepsis, and they have been questioned for being too sensitive and not specific enough, Kaukonen and colleagues[44] found that SIRS signs might not be sensitive enough. In their study, the authors found a subgroup of patients with sepsis who did not match the SIRS criteria for sepsis, and who did not satisfy two of four SIRS criteria during their first 24 h in the ICU. Despite not meeting these criteria, these patients had a high mortality risk.[44] Thus, in clinical practice, SIRS signs are not specific enough, and also not sensitive enough, to identify patients at risk of organ dysfunction.

In practice, a patient with a common cold can show several SIRS signs but is unlikely to require ICU admission. Conversely, there are conditions (such as pancreatitis and trauma) that, in the absence of infection, can cause symptoms severe enough to require ICU admission and organ support. Since these conditions can also be complicated by the acquisition of an infection, it can be difficult to discriminate between SIRS and sepsis in these contexts. Therefore, clinicians should focus mainly on identifying signs of infection and organ dysfunction.

What are these signs? The clinical presentation of sepsis depends on the site of the infection (ie, chest focus versus urinary tract focus) and on the signs and symptoms that are part of the host response. Patients often present to the emergency department with general malaise and non-specific signs, such as fever (although hypothermia can be present too), tachycardia, tachypnoea, or altered mental status. Arterial hypotension can be present, but its absence does not exclude sepsis or provide reassurance about the severity of the syndrome, as organ perfusion can already be impaired even in the context of normal blood pressure. Patients can also present with impaired gas exchange, even when the focus of infection is outside the chest, and oliguria might be present. The skin can be mottled and the capillary

refill time increased. Laboratory tests can be useful to complement the clinical examination. Clinicians should look at lactate levels, white blood cell count (leucocytosis or leucopenia), increases in plasma C-reactive protein or procalcitonin concentrations, as well as urinary function tests, liver enzymes and function tests, and coagulation.

Management

The management of sepsis and septic shock should be undertaken as a medical emergency. Screening patients for signs and symptoms of sepsis and septic shock facilitates earlier identification and intervention.[36,45] Effective treatment should focus on timely intervention, including removal of the source of infection. Aggressive assessment for an unrecognised source or undrained abscess through appropriate laboratory testing and diagnostic imaging is a critical aspect of the initial management of sepsis. In addition, early initiation of appropriate antimicrobial therapy, restoration of tissue perfusion via fluid resuscitation, and advanced interventions guided by assessment of the adequacy of resuscitation and resolution of organ dysfunction should be part of initial sepsis management.[36,46,47] Prompt intravenous access should be obtained, blood and other appropriate cultures taken, and assessment for organ dysfunction and tissue hypoperfusion done.[36,46,48]

Initial fluid resuscitation

For patients with haemodynamic instability, as defined by either hypotension (systolic blood pressure <90 mm Hg, mean arterial pressure <70 mm Hg, or a decrease in systolic blood pressure of >40 mm Hg from baseline) or elevated lactate concentration (≥4 mmol/L), the SSC recommends rapid administration of 30 mL/kg crystalloid fluids, which should be initiated within the first hour.[36,49] In paediatric sepsis, the recommendation is an initial fluid bolus (crystalloids or albumin) of 20 mL/kg, which can be repeated up to a maximum of 60 mL/kg.[50]

However, even these recommendations are not without controversy. Indeed, in resource-limited settings, fluid bolus therapy has been found to be associated with worse outcomes in children with malaria[51] and in adults with septic shock compared with standard therapy.[52] Multiple studies have compared crystalloid-based and colloid-based resuscitation, without finding a clear benefit to colloid resuscitation.[53–56] Thus, given the increased expense associated with use of colloid fluids and the increased risk of nephrotoxicity (except with albumin, which does not increase this risk),[55] initial resuscitation should use crystalloid fluids. If a colloid fluid is required then human albumin would be considered the first choice, as opposed to one of the artificial solutions.[53] Among crystalloids, there is increasing interest in the comparison of resuscitation using balanced crystalloid solutions (eg, Ringer's lactate or Hartmann's solution) with that using normal saline, and some evidence has suggested that a chloride-restrictive resuscitation strategy

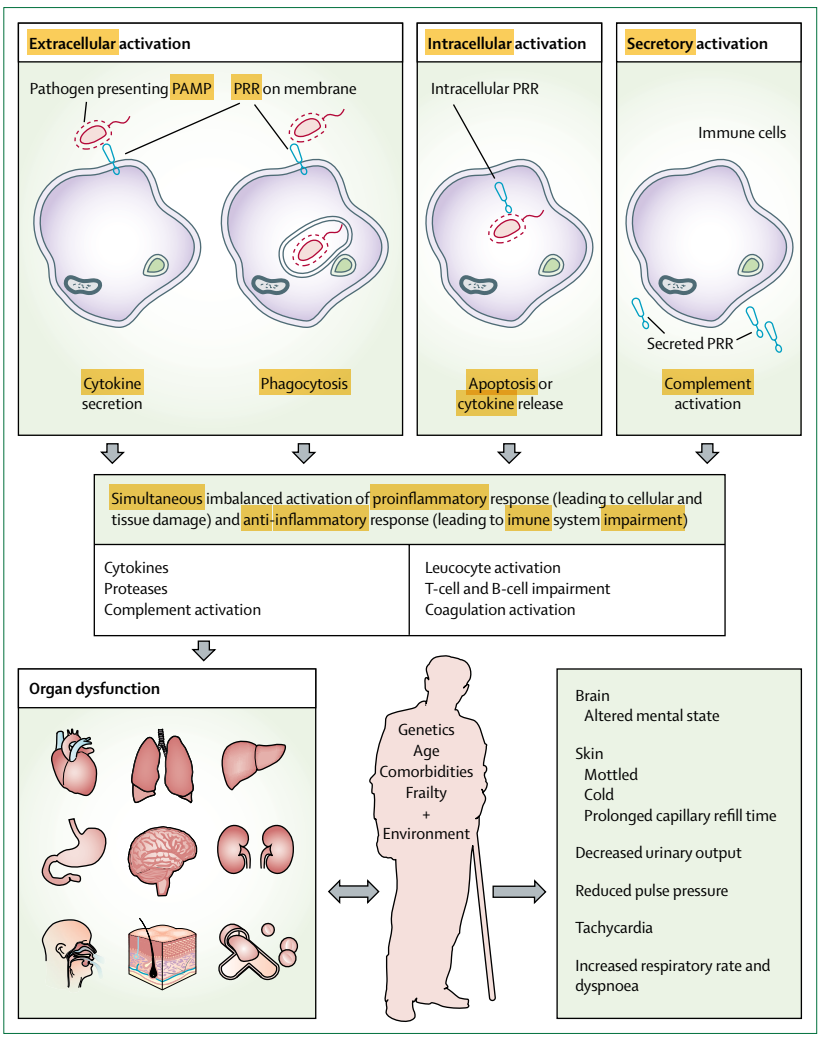

Figure: **PAMP-PRR pathways in sepsis**
PAMP=pathogen-associated molecular pattern. PRR=pattern recognition receptor.

is associated with reduced incidences of both acute kidney injury and the need for renal replacement therapy.[57] This finding has been confirmed in a large cluster-randomised study in ICUs.[58] Patients receiving balanced solutions had a lower incidence of the composite outcome (death, renal replacement therapy, or persistent renal dysfunction) compared with those receiving normal saline.[58] Notably, in another study by the same group of investigators, no difference in outcomes was observed when balanced solutions and normal saline were compared in non-critically ill patients. Two large randomised controlled trials (RCTs) investigating balanced crystalloids versus normal saline are ongoing.[59,60] However, although evidence suggests some benefits of balanced solutions in critically ill patients, there seems to be insufficient evidence to justify a complete move towards using balanced solutions instead of saline. In the meantime, it seems sensible that chloride concentrations are monitored routinely when

normal saline is used, and that a shift to a balanced crystalloid is made if hypochloraemia occurs and further fluids are needed.

Source control

Source control is the removal of infected tissue, drainage of an abscess, or removal of an infected device, and is considered best practice in the management of sepsis. Source control can be done via percutaneous drainage or open surgery. Observational data showed that inadequate early source control was associated with an increase in 28-day mortality from 26·7% to 42·9%.[36,61] As source control is a logical step in the management of sepsis, it is unlikely that future RCTs will question this standard approach.

Antibiotic therapy

Observational data from several studies of sepsis and septic shock show that timely initiation of appropriate antibiotic therapy is associated with improved patient outcomes.[62–65] Regarding patients with hypotension, a widely cited observational study showed an association between delayed antibiotic initiation and death, with a 7% increase in risk of death for every hour of delay.[63] Similar associations have been shown in patients with sepsis (with organ dysfunction and without septic shock).[64] The evidence around timing, however, is not backed by trial data, and some controversy still exists. A potentially more important question is about the appropriateness, rather than the timing, of administration. Indeed, antibiotics are not without side-effects,[66,67] and their indiscriminate use can also increase antibiotic resistance.[68] To the best of our knowledge, no trials have yet attempted to address these questions about the appropriateness of such treatments. Thus, although several studies have shown the detrimental effects of even small delays in antibiotic administration, it is important to consider antimicrobial stewardship as an essential concomitant of sepsis management, and that unnecessary antibiotic use should be avoided. Rapid de-escalation of antimicrobial therapy will allow clinicians to feel more comfortable with sepsis measures that encourage rapid administration of broad-spectrum antibiotics immediately after identification of a patient with sepsis or septic shock. The results of cultures are unlikely to be known at the time of recognition of sepsis, so the choice of antimicrobial therapy is largely empirical, and therapy should be directed against all likely pathogens because inappropriate initial therapy increases the risk of mortality.[62,69] If a specific pathogen is identified, antimicrobial therapy should be tailored accordingly.

The 2017 SSC recommendations[70] state that (1) intravenous antimicrobials should be initiated as soon as possible after the recognition of sepsis (ideally within 1 h); (2) the initial choice should include broad-spectrum cover (with either a single agent or a combination of agents); (3) the antibiotic spectrum should be narrowed when pathogens have been isolated and sensitivities established, or when clinical progress allows it; (4) dosing strategies of antimicrobials should be optimised on the basis of accepted pharmacokinetic and pharmacodynamic principles; and (5) de-escalation of antimicrobials should be considered daily and at the earliest stage when the clinical situation permits.

In the future, we will probably see an increased incidence of antibiotic resistance. Proper use of antibiotics in patients with sepsis is of paramount importance to minimise the contribution of poor antibiotic stewardship to this emerging problem. Importantly, most antibiotics are not used in people but in animals, especially in the context of the food industry.[71] For these reasons, taskforces such as the World Alliance Against Antibiotic Resistance have been established. Their aim is to define worldwide policies on the use of antibiotics. Some of these initiatives have led to the restriction of certain antibiotics for human use only.[71]

Further haemodynamic stabilisation and assessing fluid responsiveness

In patients with continued signs of haemodynamic instability after initial fluid resuscitation, fluid responsiveness should be assessed. Multiple methods for assessing and predicting fluid responsiveness have been studied, including cardiac output and stroke volume monitoring, measurement of central venous pressure, respiratory variation in inferior vena cava diameter, pulse pressure variation, and stroke volume variation.[49,72–76] All currently available methods for assessing fluid responsiveness have limitations, either in their accuracy in predicting fluid responsiveness (as for central venous pressure and central venous oxygen saturation [$ScvO_2$]), the need for advanced technology (as for pulse pressure variation and stroke volume variation), or the need for sedation, sinus rhythm, and positive pressure ventilation with tidal volumes greater than or equal to 8 mL/kg (as for inferior vena cava variability, pulse pressure variation, and stroke volume variation). Dynamic measurements, such as assessing responses in stroke volume or cardiac output to a passive leg raise, can be helpful but might be practically challenging to implement at the bedside.[77,78] When predicting fluid responsiveness with these functional haemodynamic parameters is not possible, a fluid challenge should be done to ensure fluid is given only to those patients whose haemodynamic response is favourable. Guidelines recommend that, after initial resuscitation in patients with continued hypoperfusion, fluid resuscitation should continue if there is haemodynamic improvement shown by either static or dynamic measures.[36] In these initial phases, it is very common to observe positive fluid balance. The risk of fluid overload is high and clinicians must be aware of it. Following the stabilisation phase, it is important to recognise when patients are ready for the treatment to be de-escalated. In this phase, a negative fluid balance target can be set, and diuretics are often started.[79]

Central venous oxygen saturation

Three large, multicentre RCTs[80–82] published in 2014–15 showed no benefit to protocolised early goal-directed therapy to achieve specific central venous pressure and $ScvO_2$ targets for resuscitation in settings where patients received timely initial fluid resuscitation and antibiotics. The results were confirmed in an individual patient-level meta-analysis from the same groups.[83] This finding contrasts with the results of an earlier single-centre study that showed a reduction in mortality by using a similar approach.[49] Notably, compared with this earlier study[49] baseline $ScvO_2$ values were substantially higher in the three later multicentre RCTs. The higher baseline values of $ScvO_2$ meant that early goal-directed therapy could not be delivered as the target values were mostly achieved at baseline. Although the studies might have shown different results if baseline $ScvO_2$ values had been lower, this finding highlights an important point about timing and the recognition and treatment of sepsis: patients with sepsis are recognised earlier and receive fluid resuscitation earlier than in the past, possibly because of awareness campaigns, research, and guidelines.

Blood lactate

There is some evidence that targeting the serum lactate to reduce its concentration can be used to guide resuscitation.[84–86] This approach remains controversial, however, as hyperlactataemia is not specific to tissue hypoperfusion, and the studies published to date have not found a sufficiently effective protocol that can directly influence serum lactate concentration. Raised lactate concentration remains of prognostic importance for patients with sepsis, and reductions in the concentration of this marker are associated with improved outcomes.[87] It is therefore important to repeat the measurements of blood lactate to monitor its kinetics and inform further management.[88]

Vasoactive drugs

In patients with septic shock, vasopressor support is often required to maintain perfusion pressure. A mean arterial pressure of 65 mm Hg is an appropriate initial target for most patients with septic shock requiring vasopressor support. Asfar and colleagues[89] showed that a higher mean blood-pressure target (80–85 mm Hg) was not associated with better survival compared with a lower target (65–70 mm Hg). In a secondary analysis of the same study population, patients with a history of chronic hypertension were less likely to develop acute kidney injury if managed with the higher blood-pressure target, but were also more likely to develop arrhythmias. Norepinephrine is the preferred first-line vasopressor because of its increased potency and reduced risk of arrhythmias compared with dopamine.[36,90–92] In patients with pre-existing hypertension, this target might need to be increased. Vasopressin reduces the dose of catecholamine vasopressors, but does not appear to affect patient mortality.[93–96] In a UK multicentre RCT published in 2016, vasopressin did not decrease the number of kidney failure-free days[97] compared with norepinephrine.

In 2017–18, two new vasopressors have been introduced: selepressin[98] and angiotensin II.[99] In preliminary studies, both drugs have been shown to be effective in increasing blood pressure and reducing noradrenaline dose, potentially representing a new option to reduce the use of catecholamines in septic shock. Whether this effect is reflected in improved patient outcomes remains to be demonstrated in future trials.[98,100–102]

Sepsis is frequently associated with (reversible) myocardial dysfunction.[103,104] The classic understanding of septic shock as a purely distributive shock with intact cardiac function has changed, and it is now established that cardiac dysfunction (systolic and diastolic) can be present even during the early stages of the disease.[105–107] Inotropic agents might be considered for patients with suspected cardiac dysfunction in association with inadequate cardiac output. Using inotropic agents routinely as an adjunct to standard haemodynamic therapy should be discouraged, especially in the absence of evident cardiac dysfunction.[88] A trial published in 2016 showed that routine administration of levosimendan was not superior to placebo for improving organ dysfunction in patients with septic shock, and might be associated with harm.[108]

Glycaemic control and nutritional support

A 2001 study in Leuven, Belgium, showed that tight glycaemic control, compared with the conventional treatment, was associated with significant reductions in morbidity and mortality in postsurgical ICU patients.[109] In a second Leuven study, morbidity (but not mortality) benefits were shown in a medical ICU setting.[110] However, a large multicentre trial (NICE-SUGAR) did not replicate these results, and highlighted the potential for harm due to hypoglycaemic episodes in the tight glycaemic control group.[111] The current consensus is to control glycaemia, maintaining it at less than 180 mg/dL, but to avoid tight glycaemic control.[70]

Although optimal nutritional support is important in critically ill patients, several controversies still exist. There is no definitive evidence regarding optimal timing and route of administration. Trials published in 2016 and 2018 failed to show benefits of either the enteral or the parenteral route.[112,113] Notably, data from one study showed that early enteral feeding, compared with the parenteral route, in ventilated patients with shock was associated with a greater risk of gastrointestinal complications (including gut ischaemia).[113] This finding suggests that an approach involving early enteral nutrition could be harmful in patients with shock.

Other therapies

The role of corticosteroids in patients with sepsis remains controversial. In early studies, the use of high doses of methylprednisolone[7] and subsequent lower doses of

hydrocortisone appeared to confer a benefit,[114] but this finding has not been replicated in larger studies.[115] Systematic reviews[116–118] and guidelines from the European Society of Intensive Care Medicine and the Society of Critical Care Medicine suggest some benefit of using corticosteroids in sepsis only if shock is present. There is some evidence that steroids are associated with ICU-acquired weakness,[119] and thus it is still not clear whether the clinical benefit outweighs the side-effects.[114,115,120,121] However, two large, multicentre trials showed favourable results from the use of steroids in septic shock. The first, the ADRENAL multicentre study (3800 patients), was negative for its primary outcome (mortality), but showed shorter durations of shock and ICU stay in the glucocorticoid group compared with the placebo group.[122] In the second, another large multicentre trial (1241 patients), a combination of hydrocortisone and fludrocortisone was associated with a lower all-causes 90-day mortality compared with the placebo.[123]

A restrictive haemoglobin target of 7 g/dL is appropriate for non-bleeding patients without active myocardial ischaemia.[124,125]

Although not limited to patients with sepsis, a single-centre trial published in 2016 showed worse survival rates for patients managed with a high arterial oxygen saturation target (97–100%) compared with those managed with a lower target (94–98%).[126] Similar results were reported in a study by Asfar and colleagues,[127] wherein an FiO_2 of 1 (hyperoxia) was associated with a higher mortality compared with an FiO_2 aiming at an oxygen saturation of 88–95% (normoxia).

Most of the pathophysiological pathways leading to organ dysfunction have been investigated in the search for a possible drug to modulate them. Coagulation pathways have been the subject of research with drugs such as drotrecogin alfa (activated)[128] and thrombomodulin.[129] Despite promising initial results with regard to the modulation of inflammation and coagulation with drotrecogin alfa, further multicentre RCTs were unable to confirm this benefit[128] and the drug was removed from the market. Thrombomodulin, another drug that modulates the coagulation pathway, was shown to be safe in human beings,[130] and its clinical efficacy is being studied in an RCT.[129]

Immunomodulation and mesenchymal stem cells are two of the latest developments in terms of possible therapeutic interventions. Interferon β is being studied in an RCT in patients with respiratory failure.[131] The use of mesenchymal stem cells in acute respiratory distress syndrome is also under investigation in a phase 2 trial after a phase 1 trial reported no safety concerns.[132]

Endotoxin removal via polymyxin B haemoperfusion is an novel therapeutic approach that is still under investigation, with inconsistent results: some initial trials showed an improvement in outcome,[133] whereas a more recent multicentre RCT showed a non-significant increase in mortality.[134,135]

Although it is hoped that current trials will soon yield positive results, and negative results contribute to our knowledge,[129] the paucity of positive results is disappointing and is prompting the medical community to develop new personalised research models with the aim of testing the right drugs in the right patients.

Precision medicine is eagerly anticipated in the field of sepsis and septic shock. Understanding that we are researching and treating a syndrome, rather than a specific disease, is important to advance both research and clinical improvement agendas. Some of the negative results might be explained by the highly heterogeneous populations in which sepsis treatments are tested. For example, it would be naive to assume that sepsis arising from a perforated abdomen in a 20-year-old patient would be the same entity as sepsis arising from pneumonia in an 80-year-old patient. New, adaptive trial designs have the potential to substantially improve research of sepsis. These trials can adapt in response to preliminary results (eg, by modifying inclusion and exclusion criteria, randomisation ratios, or endpoint definitions).[129]

Outcomes

Sepsis and septic shock are associated with high mortality and substantial morbidity. More than 25–30% of patients with sepsis die from the condition, with hospital mortality for septic shock approaching 40–60%.[21,23,24] More recent data suggest that mortality due to sepsis has dropped substantially over the past two decades. In almost 30 000 patients in the SSC, the overall hospital mortality for patients with severe sepsis and septic shock was 32·8%.[136] Mortality in clinical trials where patients received prompt fluid resuscitation and antibiotic therapy has also dropped, with three RCTs of early goal-directed therapy reporting mortality rates of 18–21% at 60 days[81] and 18–29% at 90 days.[80,82] It is likely that improved recognition and early intervention has contributed to the observed decrease in mortality.

Sepsis and septic shock are also associated with considerable longer-term morbidity. Many survivors are admitted to long-term acute-care facilities or skilled nursing facilities, and readmissions to acute-care hospitals are frequent.[137–141] Additionally, many survivors of sepsis report a decreased health-related quality of life and have substantial cognitive impairment and functional disability.[142–145] Thus, although survival for patients with sepsis has improved, much work remains to be done to improve long-term outcomes for these patients.

Quality-improvement initiatives and bundles

Multifaceted interventions have been shown to be more effective than single interventions for influencing behavioural change. Guidelines and education alone are unlikely to make substantial impacts, so the addition of audit and feedback systems is important. An important example of a multifaceted intervention in the ICU to

improve care is the SSC performance-improvement initiative for sepsis management.[45] This multifaceted intervention used local interdisciplinary teams, education materials, and audit and feedback of bedside compliance with the SSC sepsis measures. A study published in 2014 showed that an improved compliance with the resuscitation bundle was associated with a 9·6% absolute decline in mortality.[136] This increased compliance was associated with a statistically significant decrease in mortality that was even greater in hospitals with high compliance versus low compliance.

Although the observed worldwide improvement in survival for severe sepsis and septic shock could be related to other clinical improvements, and not necessarily those generated from the SSC, these results lend strength to the argument that performance metrics can be used to drive change in clinical behaviour and improve the quality of care, and can lead to decreased mortality in patients with severe sepsis and septic shock. Since the original report from the SSC, similar studies from individual hospital networks and national programmes have been published.[146] All these published studies showed an association between improved compliance with guideline-based sepsis bundles and survival. In 2018, the new SSC hour-1 bundle (panel 2)[147] has been adopted in the USA by the Centre for Medicare/Medicaid Services for mandated national public reporting.

However, other systemic factors, in addition to quality-improvement programmes such as the SSC, might have had an effect on the improved survival statistics. For instance, from 2000 to 2012, in 101 064 patients with severe sepsis or septic shock in ICUs in Australia and New Zealand, hospital mortality decreased from 35% to 28%, with a 47·5% relative risk reduction. In these countries, the SSC was not implemented.[148]

Controversies

The main areas of controversy surrounding the early management of sepsis are the absence of a robust definition that facilitates early identification and definitive treatment strategies, the absence of a reliable diagnostic marker, the absence of clarity as to the most effective method for guiding resuscitation, and the absence of a definitive treatment to change the course of the disease.

Sepsis is a syndrome rather than a disease, and is therefore diagnosed according to a consensus definition. The definition has been revised but, until there is a biochemical marker that can accurately diagnose and distinguish the condition and guide clinical management, current diagnosis and management are based on physiological patterns that are also associated with other disease processes.

Although many guidelines describe the resuscitation of patients with septic shock,[36,88] the specific bundle elements involved and the guidance of these processes remain controversial. There is a scarcity of evidence demonstrating that the use of advanced haemodynamic monitors to guide resuscitation results in improved patient-centred outcomes; however, many ICUs around the world use such devices. Indeed, there is still controversy regarding what intravenous fluids to use for such patients, and when and how to use vasoactive therapy. The evidence base surrounding such interventions is overall relatively weak and will remain so for the foreseeable future, as it is not being tackled by funded or completed clinical trials.

Although we now have an improved understanding of the pathophysiology underpinning the sepsis process, this knowledge has not been translated into a useful intervention that can change the course of the disease. Sepsis is associated with infection, but, despite optimisation of the use of antimicrobial agents, the treatment options are few and cannot be individualised according to how a patient is responding to the infectious insult. Many studies have tried to identify ways of modifying the inflammatory response, but all have failed thus far.[115,128] Until this absence of a definitive or disease-modifying treatment is corrected, the only available options are management of the infection and then support of failing organ systems.

Panel 2: Surviving Sepsis Campaign hour-1 bundle (2018 update)[147]

- "Measure lactate level. Re-measure if initial lactate is >2 mmol/L" (weak recommendation, low quality of evidence)
- "Obtain blood cultures prior to administration of antibiotics" (best practice statement)
- "Administer broad-spectrum antibiotics" (strong recommendation, moderate quality of evidence)
- "Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L" (strong recommendation, low quality of evidence)
- "Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg" (strong recommendation, moderate quality of evidence)

MAP=mean arterial pressure.

Conclusions

Sepsis is a common condition that is still associated with an unacceptably high mortality and, for many patients who survive, long-term morbidity. With the increased awareness of the condition and with the ongoing quality-improvement campaigns, we now have better understanding of the evidence-based approaches to managing the problem, which have contributed to improved outcomes. With more precise definitions and patient-specific profiles that can delineate an individualised management strategy for a patient's molecular and biochemical profile, outcomes could be

improved further. In the meantime, large RCTs can help us to increase our understanding of the value of commonly used but non-evidence-based treatments. The search continues for improved diagnostic techniques that can facilitate individualised management strategies, and for a pharmacological agent that can modify the disease process. Meanwhile, improved basic care driven by education and quality-improvement programmes offers the best hope of improving outcomes.

Contributors

MC and AR did the search, reviewed the selected articles, summarised the key findings and wrote the manuscript. LE and ML reviewed the selected articles, summarised the key findings and wrote the manuscript.

Declaration of interests

In the past 5 years, MC has received honoraria from Edwards Lifesciences, LiDCO, and Cheetah Medical for his consultancy work. All other authors declare no competing interests for this Seminar.

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