Sepsis for the anaesthetist

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Abstract

Sepsis is a dysregulated systemic response to infection. Morbidity and mortality of the syndrome are very high worldwide. Recent definitions have redefined criteria for sepsis. The new definition (Sepsis-3) classifies sepsis as infection with organ dysfunction (the old ‘severe sepsis’). Septic patients are at risk for secondary injuries, thus aggressive source control, resuscitation, and antibiotic therapy are the mainstays of management. Central to sepsis physiology is vasodilated shock. Many patients respond to i.v. fluid therapy. Pathophysiology also includes energy failure, or a cellular inability to oxidize fuel, and immune incompetence, often manifest by susceptibility to superinfections. Sepsis treatment is optimized by timely resuscitation and control of infection. Early recognition and resuscitation are associated with improved outcomes, although no single resuscitation end point is as good as overall patient assessment. Dynamic resuscitation metrics might be useful to avoid overinfusion of fluid therapies. Antibiotics should treat likely pathogens, with broader coverage for sicker patients (e.g. those with septic shock). Avoidance of iatrogenic injury, such as ventilator-induced lung injury from large tidal volumes, helps to prevent subsequent tissue damage and worsened systemic response. Single-agent therapies to block the systemic response have not fulfilled promise in sepsis, probably because part of the complex syndrome is adaptive. However, early aggressive care based on bundles is associated with improved outcomes. Research opportunities include understanding the role of neurological, endocrine, immune, and metabolic pathophysiology in the syndrome.

Key words: resuscitation; sepsis; shock

Sepsis, a dysregulated systemic response to infection, affects >1 million patients annually in the USA; severe sepsis accounts for ~27% of critical care admissions in the UK and >30 million patients worldwide. Of those afflicted, between 30 and 50% die. Comparatively, sepsis is not only a leading cause of death, but is also responsible for more deaths than several major cancers combined. In spite of this, advances in sepsis management have been limited.

Sepsis care is an opportunity for the anaesthetist. Septic patients come to the operating room regularly, and they need resuscitation and source control. Perioperative sepsis is deadly; 40% of cardiac arrests in the perioperative period were associated with sepsis, and these patients had a mortality of 77%. Some of these deaths might be preventable, as early recognition and treatment are associated with improved mortality. This is where perioperative specialists can make a difference. Monitoring, resuscitation, and most importantly, facilitating timely source control through procedural interventions can make a difference.

Defining sepsis

Consensus definitions of sepsis are still imperfect, but help to establish guidelines for appropriate care and inform the research agenda. Recent efforts have produced a new consensus definition, known as ‘Sepsis-3’. This definition is nimble and flexible, but does not capture every patient with sepsis. Providing ideal care requires good clinical judgement and a high level of suspicion.
Sepsis requires the presence of infection, which in the perioperative environment is not necessarily obvious. Patients with surgical pathology, such as a perforated viscus or undrained abscess, need urgent surgical intervention to avoid worsening infection and an overwhelming systemic response. Bacteria, fungi, and viruses can all cause sepsis, but the latter two can easily be missed. Sources, such as acalculous cholecystitis or even pneumonia, can be occult. Vigilance for sepsis should be a part of anaesthetists’ care of surgical patients. Combining the concepts of infection and host response means a diagnosis can be made from one perspective or the other. On the one hand, the systemic signs in these definitions should prompt a search for infection. On the other hand, the presence of a known infection leads the clinician to ask, ‘Is my infected patient septic?’ The sepsis definition, as a screening tool, performs differently depending on this perspective.

The response to sepsis shares features with the systemic response to tissue injury. The non-specific nature of this systemic response impedes timely diagnosis and confounds consensus as to disease definitions. A challenge of maintaining sensitivity (a low false-negative rate of diagnosis) at the cost of specificity (some patients will be incorrectly treated for infection) leads to the prescription of ‘sepsis’ to mean organ dysfunction in the presence of infection and host response. Previously, this subgroup was called ‘severe sepsis’, a term that is absent from the new definitions. A substantive change in the Sepsis-3 definitions is the application of ‘sepsis’ to mean organ dysfunction in the presence of infection and host response. New definitions replace the old Systemic Inflammatory Response Syndrome (SIRS) criteria in favour of a discriminator for more severe disease. Whereas SIRS defined a population with a systemic response to infection (severe infection), the new criteria specify a population with organ dysfunction, as indicated by a change in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more (Table 1). Such reclassification means that a sicker population can be tracked and studied. Both criteria emphasize the multiple ways that sepsis affects the patient, and both leverage readily available, albeit non-specific data to characterize a patient subset that is likely to have a potentially correctable yet deadly illness. Subtle elements, such as lethargy (or other mental status changes), hyperglycaemia (blood glucose >6.66 mmol litre⁻¹), and ileus, can serve as early warning markers for worsening infection and incipient sepsis.

The SIRS criteria included two or more of the following: elevated (or depressed) leucocyte count (e.g. >12 000 or <4000 cells litre⁻¹), tachypnoea (>20 bpm), tachycardia (>90 breaths min⁻¹), and fever (or hypothermia). These correlated with increased odds of having sepsis, but missed one in eight septic patients in a large review. A new and easier to use clinical score, qSOFA, uses mental status changes, tachypnoea, and low arterial blood pressure in the setting of suspected infection to establish a new screening tool for sepsis, one that appears to perform better than SIRS plus infection, identifying 68% of decedents at a cut-off of two or more criteria. Although there are substantive differences between the two definitions, both follow the overall concept of sepsis as a dysregulated host response to infection. Future research will enhance the new definitions.

Sepsis is no longer defined simply as serious infection. One substantive change in the Sepsis-3 definitions is the application of ‘sepsis’ to mean organ dysfunction in the presence of infection and host response. Previously, this subgroup was called ‘severe sepsis’, a term that is absent from the new definitions. Clinicians will continue to use this terminology as long as it continues to be a diagnostic code. It is a part of historical sepsis

<p>| Table 1 | Criteria for sepsis. The SOFA scores range from 0 to 4 points for each criterion. ICU, intensive care unit; $P_{CO_2}$, partial pressure of carbon dioxide; $Pa_O_2/F_I_O_2$, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen |</p>
<table>
<thead>
<tr>
<th>Scale</th>
<th>Criteria</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Systemic Inflammatory Response Syndrome (SIRS)</td>
<td>i. Temperature &gt;38.0 or &lt;36.0°C ii. Heart rate &gt;90 beats min⁻¹ iii. Respiratory rate &gt;20 bpm or $P_{CO_2}$ &lt;4.3 kPa iv. White blood cell count &gt;12 000 or &lt;4000 μl⁻¹, or &gt;10% band forms</td>
<td>Non-specific, misses one in eight patients with severe sepsis, and positive in &gt;50% of inpatients at least once during their hospitalization</td>
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<tr>
<td>Sequential [Sepsis-related] Organ Failure Assessment (SOFA) Score¹¹</td>
<td>i. $Pa_O_2/F_I_O_2$, respiratory support ii. Platelet count (&gt;150 × 10⁹ μl⁻¹ abnormal) iii. Bilirubin (&gt;1.2 mg dl⁻¹ abnormal) iv. Mean arterial pressure, use of dobutamine, epi-nephrine, norepinephrine v. Glasgow Coma Scale score vi. Serum creatinine, urine output</td>
<td>Scores range from 0 to 24. An increase in SOFA of ≥ 2 is used to signify organ dysfunction in Sepsis-3 definition. A cut-off of 2 or more SOFA points captured 68% of decedents outside the ICU and 98% of decedents in the ICU¹²</td>
</tr>
<tr>
<td>Quick SOFA (qSOFA) criteria</td>
<td>i. Respiratory rate ≥22 bpm ii. Altered mentation iii. Systolic blood pressure ≤100 mm Hg</td>
<td>Simple; does not require laboratory testing. Outperforms SOFA score in non-ICU populations; slightly less predictive in the ICU</td>
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<tr>
<td>Septic shock</td>
<td>i. Criteria for sepsis ii. Mean arterial pressure &lt;65 mm Hg or need for vasoressors iii. Serum lactate &gt;2 mmol litre⁻¹</td>
<td>Definition assumes the absence of hypovolaemia</td>
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research and will continue to be used in research for the foreseeable future. ‘Septic shock’ continues to be defined as the presence of a low systemic arterial pressure or elevated serum lactate concentration in spite of volume resuscitation.

Metabolic failure is a large component of the sepsis response. Metabolic signatures suggest mitochondrial dysfunction and a cellular energy failure. Such signatures might provide a way to screen for early sepsis in the future, and emphasize that mitochondrial dysfunction is a key component in the pathophysiology of sepsis. Another common feature of sepsis is immune dysfunction. Immune cell apoptosis, diminished immune function, and reactivation of latent infections have all been described in the sepsis syndrome. Septic patients can be anergic, unresponsive to vaccination, and susceptible to secondary infections.

Both metabolic and immune failures characterize chronic critical illness.

A more nuanced approach to the nature of the host response is seen in the predisposition, infection, response, and organ failure (PIRO) model, which stages sepsis in a similar manner to malignancy, emphasizing the patient, infection site, response, and organism as categories to guide prognosis and therapy. It is less nimble than scores such as qSOFA, but might be useful for identifying specific populations in clinical research.

Harm is implicit in the concept of a dysregulated host response. The response drives further injury, which can, in turn, lead to a worsened host response (Fig. 1). Progressive worsening injury can lead to organ failure and death, but also means that early aggressive therapy forestalls further injury and rescues a decompensating patient. Acutely, the response can cause cardiovascular collapse. Chronically, it leads to a state caused by repetitive or ongoing infectious insults. This state is remarkable for a pathological loss of autonomic, endocrine, and immunological functions and is characterized by recurrent complications, steady decline in organ function, and increasing dependence on external support for survival. Chronic critical illness state is an outcome to be avoided through timely treatment of sepsis as much as early shock: It remains poorly understood and is associated with a poor prognosis.

Multiple organ systems can express dysfunction during the response to sepsis (Table 2). Cardiovascular dysfunction manifests as shock; respiratory failure develops as gas-exchange abnormalities and pulmonary capillary leak; impaired function of the gastrointestinal tract includes ileus and hepatic abnormalities; renal tubular failure becomes acute kidney failure; metabolic abnormalities include hyperglycaemia, rampart protein catabolism, suppressed ketogenesis (except in diabetes mellitus type 1), and enhanced concentrations of stress hormones; and neurological dysfunction includes encephalopathy. Changes in immunological function are the most consistent. These include apoptosis of immune cells, impaired cellular immunity, and enhanced susceptibility to opportunistic infections, including many organisms associated with nosocomial infections. Reactivation of viruses, fungi, or latent bacteria can be a source of recurring or ongoing insults. Neurological abnormalities manifest commonly as delirium, but include autonomic dysfunction that can influence immune dysfunction.

<table>
<thead>
<tr>
<th>Table 2 Diagnostic features of septic shock</th>
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<tr>
<td><strong>Organ system</strong></td>
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<tr>
<td>Neurological</td>
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<td>Cardiovascular</td>
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<td>Pulmonary</td>
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<td>Gastrointestinal</td>
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<td>Urinary</td>
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<td>Haematological</td>
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<td>Endocrine and metabolic</td>
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<td>Infectious disease</td>
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**Treatment**

**Recognition**

The cornerstone of effective sepsis treatment is early recognition. Definitions notwithstanding, vigilance for subtle changes, such as hyperglycaemia, ileus, and mental status changes, and awareness of potential sources of infection (in particular, sources of iatrogenic infections, such as central venous or urinary catheters) can help clinicians to diagnose infections before the onset of a dysregulated response and subsequent tissue injury.

**Resuscitation**

Septic shock, when present, demands early and aggressive resuscitation at the same time as source control. A trial in 263 emergency department patients suggested that early resuscitation, titrated to physiological end points, improved mortality in septic shock. This same trial established that larger, early volumes of crystalloid (~5 litres) in the first 6 h were necessary to correct shock. Furthermore, invasive haemodynamic monitoring uncovered a group of patients whose shock might not
otherwise have been apparent to clinicians, supporting the need to improve recognition.

The pathophysiology of septic shock includes alterations in cardiac preload, afterload, contractility, and capillary leak. Vasoplegia is a central feature of the response. Septic shock is the most common cause of high-output, vasodilated shock. Patients can present with warm skin, bounding pulses, a wide pulse pressure, and brisk capillary refill. In patients with normal preseptic myocardial function, there is a hyperdynamic response, notable on echocardiography. Enhanced contractility, paired with low preload, means that the left ventricular cavity can nearly obliterate during systole. Ultrasonography of the inferior vena cava can demonstrate a narrow diameter, cyclic collapse, and small ventricular and diastolic volumes.

There are several causes of reduced cardiac preload. Diminished vascular tone impairs blood flow regulation. Low-flow capillary beds receive enhanced blood flow, and their downstream venous capacitance vessels engorge. Vascular circuits with a longer time constant see higher volumes of blood. The effective tank for intravascular blood volume increases, and venous return to the heart decreases. As a consequence of a degraded endothelial glycocalyx, intravascular capacity increases and serum fluids extravasate into surrounding extravascular tissue; for most, this is visible on examination as tissue oedema. Some patients sequester many litres of water, electrolytes, and proteins into interstitial tissue. At least initially, this oedema is not congestion; its presence heralds a need for resuscitation, not diuresis.

Looking at the control groups of several major sepsis trials helps to quantify patient volume requirements in sepsis. Table 3 lists resuscitation volumes from four large, randomized controlled trials of septic shock resuscitation.25–28 Aside from differences between the groups, the total volume of fluid given to the various control groups is notable. Also, differences between the groups are proportionally greater in the first 6 h than after 72 h, suggesting that the timing of fluid therapy was different between groups. Given the need to correct impaired perfusion and forestall further tissue injury, earlier administration of appropriate volumes of resuscitative fluids is important, as is recognition of end points for fluid resuscitation as a way to avoid the harm of excess volumes. No single measurement can be regarded as definitive evidence of adequate fluid resuscitation (see review in this issue).29 Rather, a combination of variables inform the clinician regarding when to slow down or stop volume infusion (Table 4). Central venous pressure, historically regarded as a useful tool for assessing volume resuscitation, poorly discriminates patients who will and will not respond to volume.30 However, a very low central venous pressure in the face of signs of inadequate perfusion is still a useful indicator for further volume infusion. Pulmonary artery catheter measurements would seem useful to inform shock resuscitation, but are not substantiated31 and might even be harmful.32

Table 3 Infused volumes from four large trials of sepsis resuscitation. Values are the mean (SD), when available; otherwise, added means. GDT, goal-directed therapy group

<table>
<thead>
<tr>
<th>Study and investigators</th>
<th>Group</th>
<th>6 h fluid total (ml)</th>
<th>72 h fluid total (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers and colleagues (2001)25</td>
<td>GDT</td>
<td>4981 (2984)</td>
<td>13 443 (6390)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3999 (2438)</td>
<td>13 358 (7729)</td>
</tr>
<tr>
<td>ARISE investigators and the ANZICS clinical trials group (2014)26</td>
<td>GDT</td>
<td>1964 (1415)</td>
<td>6238</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1713 (1401)</td>
<td>6095</td>
</tr>
<tr>
<td>ProCESS Investigators (2014)27</td>
<td>GDT</td>
<td>2805 (1957)</td>
<td>7253 (4605)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>2279 (1881)</td>
<td>6633 (4560)</td>
</tr>
<tr>
<td>ProMISe; Mouncey and colleagues (2015)28</td>
<td>GDT</td>
<td>2226 (1443)</td>
<td>5946 (3740)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>2022 (1271)</td>
<td>5844 (3651)</td>
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For some patients in septic shock, volume infusion is insufficient, such that vasoconstrictors or, in the event of impaired myocardial function, inotropes can be useful. Current recommendations are to treat vasoplegia with norepinephrine, using vasopressin and epinephrine as secondary agents, and to use dobutamine in the setting of impaired myocardial function, paired with low preload, means that the left ventricular cavity can nearly obliterate during systole. Ultrasonography of the inferior vena cava can demonstrate a narrow diameter, cyclic collapse, and small ventricular and diastolic volumes.

Table 4 Common end points for sepsis resuscitation

<table>
<thead>
<tr>
<th>End point</th>
<th>Goal</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Central venous pressure</td>
<td>≥8 mm Hg</td>
<td>Poor correlate with volume responsiveness. Low values (&lt;5 mm Hg) more informative. Best used in conjunction with change after a volume challenge</td>
</tr>
<tr>
<td>Cardiac Index</td>
<td>≥3.0 litre min⁻¹ m⁻²</td>
<td>Requires more sophisticated or invasive monitoring. Shock resuscitation should not wait for monitoring</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation</td>
<td>&gt;65%</td>
<td>Requires invasive access</td>
</tr>
<tr>
<td>Central venous oxygen saturation</td>
<td>&gt;70%</td>
<td>Requires invasive access</td>
</tr>
<tr>
<td>Pulse pressure variation</td>
<td>≤12%</td>
<td>Requires arterial access, regular rhythm, tidal volume &gt;8 ml kg⁻¹, absence of right heart failure</td>
</tr>
<tr>
<td>Lactate</td>
<td>&lt;4 mmol litre⁻¹</td>
<td>Clearance of lactate is likely to be a better resuscitation end point early in resuscitation. Confounded by epinephrine infusion</td>
</tr>
</tbody>
</table>
contractility. 38 Dopamine is no longer routinely recommended because of the potential for dysrhythmias. 39 40 Although the exact role for endocrine replacement is unclear, evidence suggests that vasopressin and glucocorticoids can be helpful in some instances. 41 Echocardiography can be particularly helpful in this setting to confirm the diagnosis and effects of treatment. Furthermore, evidence suggests that there is a subset of patients for whom right heart failure limits cardiac output and is associated with increased mortality from septic shock. 42

Source control and antibiotics
Without source control, sepsis and septic shock cannot be effectively reversed. For this reason, seeking out sources of infection and treating them with antimicrobials and drainage or debridement is as important as early diagnosis and treatment of shock. For an anaesthesia provider, this includes facilitating timely procedures in patients with surgical pathology. Understanding the anatomical source, causative pathogen, and patient condition helps to inform the pace and aggressiveness of therapy. Sending cultures as quickly as possible, preferably before administering antibiotics, helps to clarify effective sources and treatments. However, delaying appropriate antibiotics more than a short period of time in order to acquire cultures is not recommended. As sources of sepsis include indwelling vascular devices or urinary catheters, these should be evaluated for possible removal.

Evidence suggests that early therapy with antimicrobials that treat the causative organisms in sepsis improves survival. 43–45 Broad, empiric antibiotic coverage improves survival in septic shock when the organism is not known. 46 Double coverage with two antibiotics of different classes improves survival in septic shock, but such an effect has not been demonstrated in sepsis without shock. 47 This finding is also true in neutropenic patients. 48 When causative organisms are identified, it is appropriate to focus antibiotic therapy on the known pathogen, provided clinical improvement is observed. Antimicrobial decisions can, in this way, be driven by the clinical condition. More severely ill patients should receive broader antimicrobial coverage, whereas less severely ill patients are likely to benefit from more directed coverage and risk increased mortality from the additional agents. 47

Avoiding iatrogenic injuries
Given that the host response is compounded by tissue injury, avoidance of further damage is an important part of supporting the patient with sepsis. Avoidance of ventilator-induced lung injury is a way to minimize further tissue injury and can be vital to caring for the septic patient, after source control, antimicrobials, and resuscitation. Minimizing alveolar overdistension, repetitive opening and closing of alveoli, and barotrauma are the goals of ventilation, supported by data suggesting improved outcomes with low (6 mg kg⁻¹ predicted body weight) tidal volumes for patients with acute respiratory distress syndrome. 49 Newer analyses suggest that driving pressures should be optimized by adjusting tidal volumes and PEEP, because lower driving pressure best predicts survival in major studies of low tidal volume ventilation in acute respiratory distress syndrome. 50

Goal-directed therapy
Resuscitation end points are important to assure adequate resuscitation and minimize injury from the accumulation of extra administered fluids in tissues. Excessive fluid administration could exacerbate the endothelial glycocalyx lesion and vasoplegia of septic shock. 51 An early successful trial of goal-directed therapy demonstrated improved mortality with fluid, blood, and inotrope titration to haemodynamic goals and haemoglobin saturations measured in the superior vena cava. 25 Subsequent large, randomized trials 26–28 failed to replicate these findings, calling into question the role of goal-directed therapy. However, all therapy is based on goals, so emphasizing specific goals rather than a constellation of findings, including clinical gestalt, is likely to offer no benefit, especially in experienced centres. Moreover, the three negative studies may represent healthier patients, based on control group mortalities, and suggest that successful initiatives have changed the potential benefits of protocol-guided care. Taking these concerns into account, it is prudent to advocate that aggressive, titrated, goal-directed resuscitation should be a programmatic approach to the patient in septic shock, but that the goal specifics can still be at the discretion of the clinician or institution, provided they are followed over time to avoid over- and under-resuscitation.

Immune mediators
The link between inflammation, an adaptive and conserved response to injury, and the dysregulated host response in sepsis is still unclear. The metabolic, immunological and autonomic features of sepsis are likely to explain the increased organ failure and mortality. Attributing these to single inflammatory pathways is, however, an oversimplification. The sepsis literature is full of negative studies targeting inflammatory mediators. Anti-tumour necrosis factor-α antibodies have had inconsistent, worrisome effects on mortality, 47 and activated protein C showed an initial, but irreproducible effect. 53 High-dose steroids, 54 endotoxin antibodies, 55 and inhibition of the interaction between lipopolysaccharide and Toll-like receptor 4 56 all failed to gain traction as single sepsis therapeutics. Each of these agents targeted only part of a much more complicated response. Furthermore, although inflammatory markers can identify patients with worse outcomes in sepsis, 57 animal models of inflammatory impairment correlate with worse mortality, 58 59 and anti-inflammatory cytokines in trauma predict complications. 60 61 It is likely that inflammation is more important to surviving infections than it is in the evolution of the dysregulated response in sepsis.

The Surviving Sepsis Campaign
Contemporary sepsis management is inextricably linked with the Surviving Sepsis Campaign. Launched in 2004, this multinational initiative emphasized enhanced awareness and a systematic approach to sepsis resuscitation through the use of bundles. The Campaign’s recommendations were revised in 2008 and 2013, and are currently undergoing their third review. Revisions track evolution of knowledge, new literature, controversy, and the changing environment of sepsis. Of all the effects on clinical care, enhanced awareness and education are probably the most important. The Surviving Sepsis Campaign made sepsis a priority for clinicians of many specialties. Educational outreach influenced policies and local protocols. Awareness of the problem increased. It is hard to quantify the effects this has had on patients, but a study of performance improvement, based on an initiative from the Surviving Sepsis Campaign, correlated with a 6.2% absolute decrease in mortality during 39 months. 52 Compliance with specific care bundles increased
from 18% to only 25% during the intervention. This suggests that there is still substantial room for improvement or that implementation of coordinated care based on the recommendations is not a perfect fit in every work environment.

Some aspects of the Surviving Sepsis Campaign have generated criticism. Owing to an emphasis on early diagnosis and therapy, many feel that there is a substantial adverse effect of the guidelines, namely that some patients risk exposure to inappropriate antibiotics or overly aggressive fluid therapy. Busy clinicians working in uncertain circumstances may be judged on how quickly they comply with bundle components without a consideration of patient-specific factors. Although these are fair concerns, the overall emphasis on speeding sepsis recognition and therapy is valid.

Facilitating care

Given that septic patients require speedy recognition and coordinated therapy, the monitoring, resuscitative, and coordinating skills of anaesthetists are well suited to directing their care. This is true for intensive care and for the perioperative period. Anaesthesia teams can ensure timely monitoring, fluid therapy, cultures, antibiotics, and source control. In the case of sepsis requiring procedures to achieve source control, declaring a patient too sick for surgery is not an ideal option. Getting a patient to surgery quickly and safely can make a difference to morbidity and survival. Being able to resuscitate and treat at the same time is something anaesthetists can accomplish for septic surgical patients. Although rapid administration of antibiotics is crucial, sending cultures of blood, urine, and sputum before administration helps to diagnose the causative organisms. This is not a common feature of anaesthesia care, but should not be forgotten.

Generating new knowledge

Outreach and coordination have made a difference in sepsis outcomes, but a lot remains to be accomplished. For all the research and interest invested in sepsis, the best outcomes have, so far, resulted from the most fundamental interventions. What remains is a need to advance and individualize therapies, understand the full nature of the sepsis response, and improve diagnostic and therapeutic options. Our knowledge is nominally better. What we know is that there are few simple answers to how sepsis works and how to treat it. Focus on soluble mediators, such as tumour necrosis factor-α and activated protein C, has not yielded robust reproducible results. Sepsis involves the coordination of multiple organ systems and intracellular signal pathways, so a ‘magic bullet’ is not likely to be a possibility. Furthermore, the thing that does matter (early, aggressive care) works on two fronts. It treats sources of the response and the systemic aftermath of shock. Treating the triggers and responses at their onset can help.

It is clear that not all patients become septic in the same way. Models, such as PIRO, are useful constructs to help tease this out. There are many organisms that can cause sepsis, and there may be differences between them. This means that old models, such as the overwhelming systemic response to endotoxin, are oversimplifications of what happens in severe infection. It is likely that there are many organisms we fail to recognize as either primary drivers or secondary infections from the septic response; in particular, viruses and fungi. We understand that organ failure, now a part of the definition of sepsis, correlates with mortality, and that counting organ system failures helps to prognosticate. But we do not yet know exactly how these organ failures relate to one another to increase mortality, nor do we understand whether certain combinations are more important for prognostication or treatment. As an example, is it better for outcomes to optimize renal perfusion to the detriment of oxygenation? The answers to these sorts of questions are clinically relevant, mirroring disputes occurring at the bedside of critically ill patients every day. We know about immune failures and energy failures within cells, but we do not know what drives them or how they might help or harm the septic patient. To date, we know little about the therapeutic possibilities that might come from these observations. We know that the endocrine, immune, and nervous systems coordinate differently (or fail to coordinate) in the dysregulated response of sepsis, but so far have not had much success exploiting these observations. The unresolved role for glucocorticoids and the unfulfilled promise of intensive insulin therapy are as close as the medical community has come to the goal of modulating these pathways. Finally, we do not yet understand the transition that some patients make to a chronic critical illness state, or why it happens. We understand that this is a bad prognostic sign, but do not know why.

Finally, for all we have learned about sepsis and all the advances in care, we continue to confront a disease process that kills more people globally than almost any other. This observation implies that there is a lot to learn, some of which eludes our current understanding. Future progress in the management of sepsis will require innovative ideas and new perspectives.

Given that anaesthesia touches the neurosciences, resuscitation, and monitoring, sepsis is an opportunity for our profession. Both in the intensive care unit and in the operating room, anaesthetists have the chance to facilitate care, make timely interventions, and direct the investigations that will inform advances in care in the future. Sepsis is both a pragmatic and a theoretical opportunity.

Authors’ contributions

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Declaration of interest

None declared.

References


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