Sepsis for the anaesthetist

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Abstract

Sepsis is as 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,[1] afflicts >1 million patients annually in the USA;[2] severe sepsis accounts for ~27% of critical care admissions in the UK[3] and >30 million patients worldwide.[4] Of those afflicted, between 30 and 50% die.[5] [6] 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%.[7] Some of these deaths might be preventable, as early recognition and treatment are associated with improved mortality.[8] 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'.[1] 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.

Editor's key points

- Sepsis is a systemic inflammatory response to infection that is associated with organ dysfunction.
- Sepsis is a global problem with high morbidity and mortality.
- Treatment requires early recognition, goal-directed cardiovascular resuscitation, and control of infection source.

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.[9] 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 lower specificity (some patients will be incorrectly treated for sepsis) underscores older and newer definitions. Sepsis-3

replaces 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.[13] 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.[12] 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

Table 1 Criteria for sepsis. The SOFA scores range from 0 to 4 points for each criterion. ICU, intensive care unit; Pa_{CO_2}, partial pressure of carbon dioxide; Pa_{O_2}/FI_{O_2}, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen

Scale	Criteria	Comments
Systemic Inflammatory Response Syndrome (SIRS)	i. Temperature >38.0 or $<36.0\,°C$ ii. Heart rate >90 beats min^{-1} iii. Respiratory rate >20 bpm or Pa_{CO_2} <4.3 kPa iv. White blood cell count $>12\,000$ or <4000 μl^{-1}, or $>10\%$ band forms	Non-specific, misses one in eight patients with severe sepsis,[9] and positive in $>50\%$ of inpatients at least once during their hospitalization[10]
Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) Score[11]	i. Pa_{O_2}/FI_{O_2}, respiratory support ii. Platelet count ($<150 \times 10^3$ μl^{-1} abnormal) iii. Bilirubin (>1.2 mg dl^{-1} abnormal) iv. Mean arterial pressure, use of dobutamine, epinephrine, norepinephrine v. Glasgow Coma Scale score vi. Serum creatinine, urine output	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 ICU[12]
Quick SOFA (qSOFA) criteria	i. Respiratory rate ≥ 22 bpm ii. Altered mentation iii. Systolic blood pressure ≤ 100 mm Hg	Simple; does not require laboratory testing. Outperforms SOFA score in non-ICU populations; slightly less predictive in the ICU
Septic shock	i. Criteria for sepsis ii. Mean arterial pressure <65 mm Hg or need for vasopressors iii. Serum lactate >2 mmol litre^{-1}	Definition assumes the absence of hypovolaemia

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.[14] 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.[15][16] Another common feature of sepsis is immune dysfunction. Immune cell apoptosis,[17] diminished immune function,[18] and reactivation of latent infection[19] have all been described in the sepsis syndrome. Septic patients can be anergic, unresponsive to vaccination, and susceptible to secondary infections.[19][20] 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,[21] 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[22] 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.
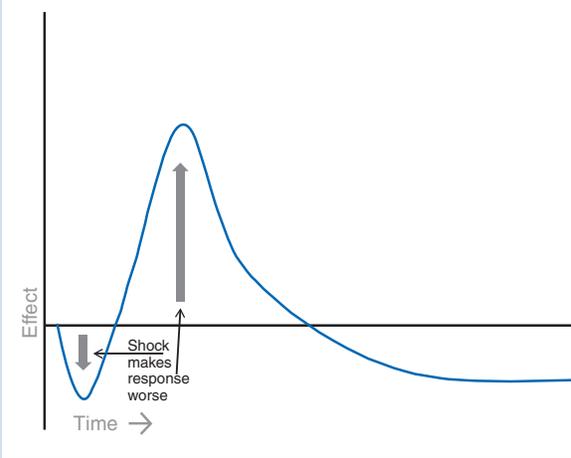

Fig 1 Stress response to injury. Hypoperfusion in early septic shock creates tissue injury that exacerbates the later vasodilated response. This can lead to a return to hypoperfusion and a state of shock.

Table 2 Diagnostic features of septic shock

Organ system	Alteration or dysfunction
Neurological	Delirium, altered mental status
Cardiovascular	Vasodilation, hypovolaemia (early), cardiac dysfunction
Pulmonary	Tachypnoea, poor gas exchange, acute respiratory distress syndrome
Gastrointestinal	Ileus, hyperbilirubinaemia
Urinary	Oliguria, elevated plasma urea and creatinine
Haematological	Anaemia, thrombocytopenia, coagulopathy, disseminated intravascular coagulation
Endocrine and metabolic	Hyperglycaemia, sick euthyroid syndrome, elevated lactate
Infectious disease	Leucocytosis, elevated inflammatory mediators

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, rampant 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.[19][20] Neurological abnormalities manifest commonly as delirium, but include autonomic dysfunction that can influence immune dysfunction.[23][24]

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.[25] 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 substantiated[31] and might even be harmful.[32] Previously, a therapeutic strategy of supra-normal oxygen delivery (of the order of $666 \, \text{ml} \, O_2 \, \text{min}^{-1} \, \text{m}^{-2}$)[33] was proposed as a way to treat an oxygenation 'deficit' that was believed to be the cause of subsequent organ failure in septic patients. The validity of this approach is questioned by a failure to reproduce research outcomes and a suggestion that the driving conceptual observation, supply-dependent oxygen consumption, is in fact an artifact of the measuring strategy.[34] Newer measures of volume responsiveness, such as pulse pressure variation, might provide a more dynamic and realistic tool to help clinicians weigh the risks and benefits of further volume administration.[25 35] Markers of tissue perfusion and the mismatch between oxygen supply and demand, such as mixed venous oxygen saturation or serum lactate concentrations, can be helpful.[36 37]

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

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

Study	Group	6 h fluid total (ml)	72 h fluid total (ml)
Rivers and colleagues (2001)[25]	GDT	4981 (2984)	13 443 (6390)
	Control	3499 (2438)	13 358 (7729)
ARISE investigators and the ANZICS clinical trials group (2014)[26]	GDT	1964 (1415)	6238
	Control	1713 (1401)	6095
ProCESS Investigators (2014)[27]	GDT	2805 (1957)	7253 (4605)
	Control	2279 (1881)	6633 (4560)
ProMISe; Mouncey and colleagues (2015)[28]	GDT	2226 (1443)	5946 (3740)
	Control	2022 (1271)	5844 (3651)

Table 4 Common end points for sepsis resuscitation

End point	Goal	Comment
Central venous pressure	$\geq 8 \, \text{mm Hg}$	Poor correlate with volume responsiveness. Low values ($<5 \, \text{mm}$ Hg) more informative. Best used in conjunction with change after a volume challenge
Cardiac Index	$\geq 3.0 \, \text{litre} \, \text{min}^{-1} \, \text{m}^{-2}$	Requires more sophisticated or invasive monitoring. Shock resuscitation should not wait for monitoring
Mixed venous oxygen saturation	$>65\%$	Requires invasive access
Central venous oxygen saturation	$>70\%$	Requires invasive access
Pulse pressure variation	$\leq 12\%$	Requires arterial access, regular rhythm, tidal volume $>8 \, \text{ml} \, \text{kg}^{-1}$, absence of right heart failure
Lactate	$<4 \, \text{mmol} \, \text{litre}^{-1}$	Clearance of lactate is likely to be a better resuscitation end point early in resuscitation. Confounded by epinephrine infusion

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,[52] 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.[62] 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 signaling 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.[11] 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 bedsides 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

Writing and revision: M.E.N.

Declaration of interest

None declared.

References

1. Singer M, Deutschman CS, Seymour CW, *et al*. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 801–10
2. Hall MJ, Williams SN, DeFrances CJ, Golosinskiy A. Inpatient care for septicemia or sepsis: a challenge for patients and hospitals. *NCHS Data Brief* 2011; **62**: 1–8
3. Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Crit Care* 2006; **10**: R42
4. Fleischmann C, Scherag A, Adhikari NK, *et al*. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. *Am J Respir Crit Care Med* 2016; **193**: 259–72
5. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United

States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; **29**: 1303–10

6. Wood KA, Angus DC. Pharmacoeconomic implications of new therapies in sepsis. *Pharmacoeconomics* 2004; **22**: 895–906

7. Kazaure HS, Roman SA, Rosenthal RA, Sosa JA. Cardiac arrest among surgical patients: an analysis of incidence, patient characteristics, and outcomes in ACS-NSQIP. *JAMA Surg* 2013; **148**: 14–21

8. Levy MM, Dellinger RP, Townsend SR, *et al*. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010; **38**: 367–74

9. Cuthbertson D, Tilstone WJ. Metabolism during the postinjury period. *Adv Clin Chem* 1969; **12**: 1–55

10. Churpeck MM, Zadravecz FJ, Winslow C, Howell MD, Edelson DP. Incidence and prognostic value of the systemic inflammatory response syndrome and organ dysfunctions in ward patients. *Am J Respir Crit Care Med* 2015; **192**: 958–64

11. Vincent JL, Moreno R, Takala J, *et al*. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707–10

12. Seymour CW, Liu VX, Iwashyna TJ, *et al*. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**: 762–74

13. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. *N Engl J Med* 2015; **372**: 1629–38

14. Langley RJ, Tsalik EL, van Velkinburgh JC, *et al*. An integrated clinico-metabolomic model improves prediction of death in sepsis. *Sci Transl Med* 2013; **5**: 195ra95

15. Brealey D, Karyampudi S, Jacques TS, *et al*. Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. *Am J Physiol Regul Integr Comp Physiol* 2004; **286**: R491–7

16. Levy RJ, Vijayasarathy C, Raj NR, Avadhani NG, Deutschman CS. Competitive and noncompetitive inhibition of myocardial cytochrome C oxidase in sepsis. *Shock* 2004; **21**: 110–4

17. Hotchkiss RS, Swanson PE, Freeman BD, *et al*. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. *Crit Care Med* 1999; **27**: 1230–51

18. Heidecke CD, Hensler T, Weighardt H, *et al*. Selective defects of T lymphocyte function in patients with lethal intraabdominal infection. *Am J Surg* 1999; **178**: 288–92

19. Limaye AP, Kirby KA, Rubenfeld GD, *et al*. Cytomegalovirus reactivation in critically ill immunocompetent patients. *JAMA* 2008; **300**: 413–22

20. Luyt CE, Combes A, Nieszkowska A, Trouillet JL, Chastre J. Viral infections in the ICU. *Curr Opin Crit Care* 2008; **14**: 605–8

21. Levy MM, Fink FP, Marshall JC, *et al*. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; **31**: 1250–6

22. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. *Am J Respir Crit Care Med* 2010; **182**: 446–54

23. Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. *J Clin Invest* 2007; **117**: 289–96

24. Deutschman CS, Raj NR, McGuire EO, Kelz MB. Orexinergic activity modulates altered vital signs and pituitary hormone secretion in experimental sepsis. *Crit Care Med* 2013; **41**: e368–75

25. Rivers E, Nguyen B, Havstad S, *et al*. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**: 1368–77

26. ARISE investigators and the ANZICS clinical trials group. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; **371**: 1496–506

27. ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014; **370**: 1683–93

28. Mouncey PR, Osborn TM, Power GS, *et al*. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med* 2015; **372**: 1301–11

29. Meng L, Heerdt PM. Perioperative goal-directed haemodynamic therapy based on flow parameters: a concept in evolution. *Br J Anaesth* 2016; **117(Suppl 3)**: iii3–17

30. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and plea for some common sense. *Crit Care Med* 2013; **41**: 1774–81

31. Sandham JD, Hull RD, Brant RF, *et al*. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003; **348**: 5–14

32. Connors AF, Speroff T, Dawson NV, *et al*. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA* 1996; **276**: 889–97

33. Shoemaker WC, Appel PL, Kram HB. Role of oxygen debt in the development of organ failure sepsis, and the death in high-risk surgical patients. *Chest* 1992; **102**: 208–15

34. Manthous CA, Schumacker PT, Pohlman A, *et al*. Absence of supply dependence of oxygen consumption in patients with septic shock. *J Crit Care* 1993; **8**: 203–11

35. Michard F, Boussat S, Chemla D, *et al*. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med* 2000; **162**: 134–8

36. Jones AE, Shapiro NI, Trzeciak S, *et al*. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA* 2010; **303**: 739–46

37. Nguyen HB, Kuan WS, Batech M, *et al*. Outcome effectiveness of the severe sepsis resuscitation bundle with addition of lactate clearance as a bundle item: a multi-national evaluation. *Crit Care* 2011; **15**: R229

38. Dellinger RP, Levy MM, Rhodes A, *et al*. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013; **39**: 165–228

39. De Backer D, Biston P, Devriendt J, *et al*. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; **362**: 779–89

40. Vasu TS, Cavallazzi R, Hirani A, Kaplan G, Leiby B, Marik PE. Norepinephrine or dopamine in septic shock: systematic review of randomized clinical trials. *J Intensive Care Med* 2012; **27**: 172–8

41. Russell JA, Walley KR, Gordon AC, *et al*. Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. *Crit Care Med* 2009; **37**: 811–8

42. Furian T, Aguiar C, Prado K, *et al*. Ventricular dysfunction and dilation in severe sepsis and septic shock: relation to endothelial function and mortality. *J Crit Care* 2012; **27**: 319.e9–5

43. Zhang D, Micek S, Kollef MH. Time to appropriate antibiotic therapy is an independent determinant of postinfection ICU and hospital lengths of stay in patients with sepsis. *Crit Care Med* 2015; **43**: 2133–40

44. Kumar A, Roberts D, Wood KE, *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; **34**: 1589–96

45. Ferrer R, Martin-Loeches I, Phillips G, *et al*. Empiric antibiotic treatment reduces mortality in severe sepsis and septic

shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med* 2014; **42**: 1749–55

46. Kumar A, Zarychanski R, Light B, *et al*. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. *Crit Care Med* 2010; **38**: 1773–85

47. Paul M, Lador A, Grozinsky-Glasberg S, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev* 2014; **1**: CD003344

48. Paul M, Dickstein Y, Schlesinger A, Grozinsky-Glasberg S, Soares-Weiser K, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. *Cochrane Database Syst Rev* 2013; **6**: CD003038

49. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; **342**: 1301–8

50. Amato MD, Meade MO, Slutsky AS, *et al*. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015; **372**: 747–55

51. Marik P, Bellomo R. A rational approach to fluid therapy in sepsis. *Br J Anaesth* 2016; **116**: 339–49

52. Abraham E, Wunderink R, Silverman H, *et al*. Efficacy and safety of monoclonal antibody to human tumar necrosis factor α in patients with sepsis syndrome. A randomized, controlled, double-blind, multicenter clinical trial. TNF-alpha MAb Sepsis Study Group. *JAMA* 1995; **273**: 934–41

53. Ranieri VM, Thompson BT, Barie PS, *et al*. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; **366**: 2055–64

54. Bone RD, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987; **317**: 653–8

55. McCloskey RV, Straube RC, Sanders C, Smith SM, Smith CR. Treatment of septic shock with human monoclonal antibody HA-1A. A randomized, double-blind, placebo-controlled trial. CHESS Trial Study Group. *Ann Intern Med* 1994; **121**: 1–5

56. Matsuyama K, Eisai's severe sepsis drug fails in final-state study. 2011. Available from http://www.bloomberg.com/news/articles/2011-01-25/eisai-s-sepsis-drug-eritoran-fails-to-save-more-lives-in-final-stage-study (accessed 26 September 2016)

57. Staniek K, Gille L, Kozlov AV, Nohl H. Mitochondrial superoxide radical formation is controlled by electron bifurcation to the high and low potential pathways. *Free Radic Res* 2002; **36**: 381–7

58. Marino MW, Dunn A, Grail D, *et al*. Characterization of tumor necrosis factor-deficient mice. *Proc Natl Acad Sci USA* 1997; **94**: 8093–8

59. Amiot F, Fitting C, Tracey KJ, Cavaillon JM, Dautry F. Lipopolysaccharide-induced cytokine cascade and lethality in LT alpha/TNF alpha-deficient mice. *Mol Med* 1997; **3**: 864–75

60. Neidhardt R, Keel M, Steckholzer U, *et al*. Relationship of interleukin-10 plasma levels to severity of injury and clinical outcome in injured patients. *J Trauma* 1997; **42**: 863–70

61. Sherry RM, Cue JI, Goddard JK, Parramore JB, DiPiro JT. Interleukin-10 is associated with the development of sepsis in trauma patients. *J Trauma* 1996; **40**: 613–6.

62. Levy MM, Dellinger RP, Townsend SR, *et al*. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med* 2010; **36**: 222–31