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STATE OF THE ART REVIEW

Sepsis: pathophysiology and clinical management

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ABSTRACT

Sepsis, severe sepsis, and septic shock represent increasingly severe systemic inflammatory responses to infection. Sepsis is common in the aging population, and it disproportionately affects patients with cancer and underlying immunosuppression. In its most severe form, sepsis causes multiple organ dysfunction that can produce a state of chronic critical illness characterized by severe immune dysfunction and catabolism. Much has been learnt about the pathogenesis of sepsis at the molecular, cell, and intact organ level. Despite uncertainties in hemodynamic management and several treatments that have failed in clinical trials, investigational therapies increasingly target sepsis induced organ and immune dysfunction. Outcomes in sepsis have greatly improved overall, probably because of an enhanced focus on early diagnosis and fluid resuscitation, the rapid delivery of effective antibiotics, and other improvements in supportive care for critically ill patients. These improvements include lung protective ventilation, more judicious use of blood products, and strategies to reduce nosocomial infections.

Introduction

Sepsis is a common, deadly, and expensive disease worldwide. Although sepsis has long been recognized, it was not clinically defined until the late 20th century, mainly because the lack of effective antimicrobials and supportive care prevented patients with sepsis from surviving long enough to be studied or to develop sequelae of organ dysfunction. As care and outcomes improved, the need for more precise terminology became evident both for clinicians and for researchers designing clinical trials.[1] In the early 1990s, a consensus statement was developed by the American College of Chest Physicians and the Society of Critical Care Medicine (SCCM) that defined systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock in terms of both clinical and laboratory abnormalities (fig 1),[2] emphasizing a continuum of acute inflammation and organ dysfunction. Revised modestly in 2001,[4] these definitions have formed the basis of the past quarter century of research into sepsis and catalyzed the evolution of its clinical recognition and management, and the design of clinical trials. However, the sensitivity and specificity of SIRS criteria have been questioned,[5 6] as has the contention that SIRS, sepsis, severe sepsis, and septic shock occur along a continuum rather than as discrete clinical entities.[7] In February 2016, the European Society of Intensive Care Medicine and the SCCM published new consensus definitions of sepsis and related clinical criteria (fig 1; Sepsis-3[3]). The most important changes were:

- The terms SIRS and severe sepsis were eliminated
- Sepsis is now defined as life threatening organ dysfunction caused by a dysregulated host response to infection
- Organ dysfunction is newly defined in terms of a change in baseline SOFA (sequential organ failure assessment) score
- Septic shock is defined as the subset of sepsis in which underlying circulatory and cellular or metabolic abnormalities are profound enough to increase mortality substantially.

Novel mechanistic insights about sepsis have not yet translated into specific drug treatments. However, mortality has declined even as the severity and incidence of sepsis have risen. In this review, which is aimed at specialists in critical care and related areas, we critically review the past 35 years of published studies on the epidemiology, risk factors, microbiology, pathogenesis, and treatment of sepsis.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

A 20 year old survivor of severe pneumococcal sepsis and acute respiratory distress syndrome who required a lung transplant, as well as his mother, kindly accepted an invitation to review the manuscript as patient reviewers for *The BMJ*. They were asked to indicate which sections or information were of greatest importance and relevance to them and which sections were the least useful. Alternatively, or in addition, they could write general comments about what they thought was missing or underemphasized. As a result of their input, we clarified several areas of the article and put more emphasis on the role of vaccines in preventing illness and on improvements in supportive critical care.

Category	Definition
PREVIOUS DEFINITIONS	
SIRS (systemic inflammatory response syndrome)	Two of the following: • Temperature >38°C or <36°C • Heart rate > 90 beats/min • Respiratory rate >20 breaths/min or arterial carbon dioxide pressure <32 mm Hg • White blood cell count >12×10⁹/L or <4×10⁹/L
Sepsis	SIRS with infection (presumed or proven)
Severe sepsis	Sepsis with evidence of acute organ dysfunction (hypotension, lactic acidosis, reduced urine output, reduced PaO_2/FIO_2 ratio, raised creatinine or bilirubin, thrombocytopenia, raised international normalized ratio)
Septic shock	Sepsis with persistent hypotension after fluid resuscitation
REVISED DEFINITIONS	
Sepsis	Life threatening organ dysfunction* caused by a dysregulated host response to infection
Septic shock	Sepsis and vasopressor therapy needed to increase mean arterial pressure to ≥65 mm Hg and lactate to >2 mmol/L despite adequate fluid resuscitation

Fig 1 | Previous[2] and recently revised[3] definitions of sepsis and related syndromes. *As assessed by an acute change of ≥2 points in the sequential organ failure assessment score (components: partial pressure of oxygen in arterial blood/fractional inspired oxygen (PaO_2/FIO_2) ratio, Glasgow coma scale, mean arterial pressure, vasopressor use, serum creatinine or urine output, bilirubin, and platelet count). We used the previous definitions in this review because they are central to the understanding of the past quarter century of research into the epidemiology, pathogenesis, and treatment of sepsis, including all ongoing clinical trials

Sources and selection criteria

We identified references for this review through searches of publications listed by PubMed from 1980 to 23 February 2016. We used the search terms "sepsis", "septic", "SIRS", "infection", "epidemiology", "pathophysiology", "microbiology", "resuscitation", "history", "treatment", "therapy", "cancer", "malignancy", "age", "ethnicity", "race", "immunosuppression", "genetic", "endothelial", "epithelial", "coagulopathy", "cytokine", "guidelines", and "resolution". References were also identified from relevant review articles. We looked at in vitro, animal, and human studies, including meta-analyses. Only articles published in English were reviewed. We screened more than 5000 articles of evidence classes I-IV and included classes I-III. We excluded articles published in non-peer reviewed journals, case reports, and small uncontrolled series. The final reference list was based on relevance to the topics covered in the review.

Epidemiology

Over the past 40 years the incidence of severe sepsis has substantially increased, partly because of the increasing age of the population. The latest estimates in the United States, Europe, and the United Kingdom range between 0.4/1000 and 1/1000 of the population.[8-12] Remarkably, in-hospital mortality for patients with sepsis during this period has decreased from 28% to 18%.[9] A recent study that used a database of prospectively collected data from more than 90% of all intensive care unit (ICU) admissions in Australia and New Zealand between 2000 and 2012 confirmed these trends in both incidence and mortality.[13] Using objective definitions of acute organ dysfunction, severe sepsis in patients admitted to the ICU was estimated to increase from 7.2% to 11.1% during the study period. At the same time, hospital mortality in severe sepsis declined from 35% to 18%, an improvement that persisted across different severities of illness, geographic regions, and hospital types and sizes. Cumulatively, the highest quality epidemiologic studies indicate that severe sepsis is becoming both more common and less deadly.

Host differences in the incidence and outcome of sepsis

Demographics

Women have a lower incidence of severe sepsis, yet mortality results are mixed.[8-16] The causes of this sex difference remain unexplained but may involve the effect of sex hormones on innate and adaptive immunity and on the cardiovascular response to cytokine signaling.[17] Race seems to be another important risk factor for sepsis. The incidence of sepsis in the US is higher in non-whites (relative risk 1.9), especially African-Americans.[9] Similar results were reported in a subset of US states,[18] and in a separate detailed analysis from New Jersey.[19] Possible explanations for these differences include disparities in access to timely healthcare, immunizations, poverty, and comorbidities including HIV, diabetes, chronic kidney disease, and substance use disorders.[18-20] However, the increased incidence of infection and organ dysfunction in patients of African descent seems to persist after controlling for many of these factors, suggesting that genetic factors may also be involved.[20-22]

Older patients are far more likely to develop sepsis. A study of discharge data from 500 US hospitals reported that patients 65 years and older comprised 12% of the population but nearly 65% of sepsis cases (relative risk 13.1).[23] Older patients were twice as likely to have comorbid conditions, but a multivariate analysis that adjusted for these conditions in addition to race, sex, source of infection, and severity of illness found that patients with sepsis who were aged 65 or more were 2.3 times more likely to die. Furthermore, patients who survived were less likely to be discharged home. A more recent study

published in 2014 focused on longer term mortality in patients 65 years or more treated for severe sepsis in the US Veterans Affairs healthcare system in the mid-2000s.[24] Of the 40% of patients who survived for at least 90 days after the initial episode, an additional 31% had died by one year and 43% by two years, with the highest mortality associated with comorbid cirrhosis or metastatic cancer. Thus, advancing age is a strong risk factor for the incidence of sepsis and mortality from sepsis, and this is explained in part by the presence of comorbid conditions. Accordingly, the aging of the population probably explains much of the rising incidence of sepsis in industrialized societies.

Immunosuppression and cancer

Conditions that suppress innate and adaptive immunity are risk factors for sepsis. A multicenter study of sepsis in French ICUs estimated that immunosuppression was associated with an increased incidence of severe sepsis (odds ratio 2.8).[25] Chronic conditions that suppress the immune system—including HIV/AIDS, cirrhosis, asplenia, and autoimmune disease—are heavily represented in large epidemiologic studies of patients with sepsis.[8-27] An observational study published in 2014 of patients admitted to 11 French ICUs between 1997 and 2011 with severe sepsis or septic shock found that 31% were immunocompromised from AIDS, solid organ transplantation, neutropenia, solid or hematologic cancer without neutropenia, inflammatory disorder, and primary immunodeficiency.[28] Only AIDS, neutropenia, and cancer were independent risk factors for 28 day mortality compared with immunocompetent patients.

Patients with cancer are often immunosuppressed, from both the cancer and its treatment. An analysis of ICD-9 (international classification of diseases, 9th revision) codes from six US states found that patients with cancer had a relative risk for severe sepsis of nearly 4 (16.4 cases/1000 cancer population), along with 52% higher hospital mortality (38% *v* 25%), and a three times longer hospital stay compared with patients without cancer.[29] Patients with lung and hematologic cancers fared the worst. An analysis of 563 patients with cancer admitted with sepsis to a single Brazilian ICU between 2003 and 2007 reported 67% mortality at six months in patients with severe sepsis.[30] The best predictors of mortality included low performance status (odds ratio 3.6), recurrence or progression of cancer (2.4), infectious source other than urine (3.3), and respiratory (2.3) or renal (2.1) impairment. Similarly, a retrospective analysis of patients with cancer admitted with septic shock to 41 French ICUs between 1997 and 2008 identified mechanical ventilation (5.5), renal replacement therapy (1.7), and fungal infection (2.0) as independent risk factors for mortality.[31] This study also reported a steep decline in ICU mortality in patients with cancer and septic shock from 70% in 1997 to 53% in 2008, and made the important observation that outcomes were better in high volume centers.

Genetic variants

A landmark study of more than 1000 people who had been adopted in the 1920s to the 1940s in Denmark reported a remarkable increase in the risk of death by infection before the age of 50 if a biological parent died of an infectious cause (relative risk 5.8 (95% confidence interval 2.4 to 13.7) *v* 0.7 (0.1 to 5.4) for an adoptive parent).[32] Although generated in an era before the widespread use of antibiotics, these data provide strong evidence that the tendency to succumb to overwhelming infection is in part heritable. A limited number of patients have congenital immunodeficiencies related to defects in innate and adaptive immune processes, including pattern recognition receptors, complement, cytokines, and effector cells.[33] Despite an extensive search for more common and subtle genetic variants that predispose to sepsis, only a few candidates have been found. Genome-wide association studies in patients with sepsis have been difficult given challenges in the definition of sepsis and the consequent heterogeneity of these patients.[34-36]

Polymorphisms in Toll-like receptor 4 (TLR4) and TLR1 have been associated with increased susceptibility to Gram negative septic shock,[37 38] candidemia,[39 40] and invasive aspergillosis.[41] Interestingly, the Asp299Gly TLR4 polymorphism may confer protection against cerebral malaria. This could explain its increased frequency in people from sub-Saharan Africa,[22] and it might be related to ethnic differences in the incidence and severity of sepsis. NOD2 (nucleotide binding oligomerization domain containing protein 2) and the Asp299Gly variants were additive in increasing the risk of bacteremia and hospital mortality in a study of nearly 800 Belgian ICU patients.[42] A genome-wide association study of 520 patients with septic shock of European ancestry from 27 ICUs from North America and Australia identified only one single nucleotide polymorphism that was associated with increased 28 day mortality and organ dysfunction. This was the C allele of *SVEP1* (11% allele frequency in European populations), which encodes a cell adhesion molecule with multiple domains capable of interacting with complement, growth factors, integrins, and cytokines.[43] Finally, in a recent genome-wide association study involving four cohorts of 2500 patients admitted to 143 European ICUs with sepsis, severe sepsis, and septic shock from pneumonia or intra-abdominal infection, a common (20%) variant of the *FER* gene (Fps/FES related tyrosine kinase, a cytosolic protein thought to be involved in leukocyte recruitment) was associated with increased survival, although only in patients with pneumonia.[44]

Modifiable risk factors

Alcohol consumption has been shown in adjusted epidemiologic analyses to increase the risk of sepsis and related organ failure and mortality.[45 46] Although tobacco is now a well established risk factor for acute respiratory distress syndrome (ARDS),[47 48] evidence linking smoking to sepsis has been less robust. In a study of 30 000 outpatients observed for a five year period during which 975 cases of sepsis were detected, tobacco use was significantly associated with incident sepsis (hazard ratio 1.9).[49] Cigarette smoking has been associated with a several-fold increase in the risk of invasive pneumococcal disease,[50] and it has been shown to increase the risk of septic shock (odds ratio 2.1) and 30 day mortality (5.0) in pneumo-

Organism	Western Europe	Eastern Europe	Central/ South America	North America	Oceania	Africa	Asia
Staphylococcus aureus/MRSA	20/9	22/10	19/11	27/18	28/9	30/20	16/10
Staphylococcus epidermidis	11	12	9	12	8	15	9
Streptococcus pneumoniae	5	5	3	4	3	6	2
VSE	9	10	2	5	4	0	4
VRE	4	5	2	5	5	0	2
Escherichia coli	17	15	14	14	13	11	17
Enterobacter spp	7	8	9	8	3	7	5
Klebsiella spp	10	21	16	9	12	19	21
Pseudomonas spp	17	29	26	13	15	15	29
Acinetobacter spp	6	17	14	4	4	15	19
ESBL producing GNR	2	2	3	0	0	2	3
Anaerobes	5	3	1	8	3	2	3
Candida spp	19	19	13	18	13	11	16
Aspergillus spp	2	0	0	3	2	0	1
Parasites	1	1	1	1	1	0	1

Fig 2| Common microbiological isolates from the Extended Prevalence of Infection in Intensive Care (EPIC II; % of isolates).[58] Abbreviations: MRSA=methicillin resistant *Staphylococcus aureus*; VRE=vancomycin resistant enterococcus; VSE=vancomycin sensitive enterococcus; ESBL=extended spectrum β-lactamase. Darker boxes indicate prevalence significantly different from that seen in western Europe

coccal pneumonia.[51 52] Smoking also seems to predispose patients to postoperative infections.[53 54] A meta-analysis in 2013 also found that vitamin D deficiency increases the risk of sepsis (relative risk 1.46),[55] although whether supplementation mitigates this risk remains unclear.[56] Finally, vaccination has been shown to reduce the incidence of sepsis caused by specific pathogens, including *Haemophilus influenzae*.[57]

Causes

Non-infectious

The term SIRS captures those patients who develop a clinical picture of sepsis without an identifiable infection (fig 1).[2] Many of these patients subsequently develop evidence of infection, but several sterile inflammatory conditions can also progress to shock and multiorgan failure. These include pancreatitis, tissue ischemia, trauma and surgical tissue injury, burns, thromboembolism, vasculitis, drug reactions (including neuroleptic malignant syndrome), and autoimmune and neoplastic processes such as lymphoma and hemophagocytic lymphohistiocytosis.

Infectious

The Extended Prevalence of Infection in Intensive Care (EPIC II) study gathered extensive demographic, physiological, bacteriological, therapeutic, and outcome data from more than 14 000 adult patients in 1265 ICUs from 75 countries on a single day in May 2007,[58] and it provides the best recent evidence on the infectious causes of sepsis. Of the 7000 patients classified as infected, the site of infection was most commonly the lungs (64%), followed by the abdomen (20%), bloodstream (15%), and renal or genitourinary tract (14%). Of the 70% of infected patients with positive microbiology, 47% of isolates were Gram positive (*Staphylococcus aureus* alone accounted for 20%), 62% Gram negative (20% *Pseudomonas* spp and 16% *Escherichiacoli*), and 19% fungal. Prevalence data are notably limited by the ability to grow and identify organisms using standard microbiologic techniques. For example, *Streptococcus pneumoniae* is thought to be the most common cause of bacterial pneumonia worldwide, yet it is not often identified in clinical specimens.[59] Interestingly, major regional differences in the prevalence of certain drug resistant organisms were described (fig 2), including methicillin resistant *S aureus* (MRSA) and strains of *Klebsiella*, *Pseudomonas*, and *Acinetobacter*.

Several groups have studied the EPIC II data to generate important additional insights into the microbiology of sepsis. Of the 14 000 patients, 99 had candida bloodstream infections, and these patients had much higher ICU mortality (43% *v* 25-29%) and length of hospital stay than patients with bacteremia.[60] MRSA infections have been independently associated with a hospital mortality nearly 50% higher than methicillin sensitive *Saureus* ones.[61] However, a separate analysis reported that after adjusting for covariates, patients admitted to ICUs in countries with a high prevalence of MRSA and other drug resistant pathogens did not fare worse than those admitted to ICUs in countries with less resistant pathogens.[62] Of the 20% of patients with sepsis and an abdominal infectious source, 64% had undergone emergency surgery, and 67% had positive microbiology, most often Gram negative bacteria

(48%).[63] ICU mortality was highest for abdominal sepsis (29%), and independent mortality predictors included hematologic cancer, cirrhosis, mechanical ventilation, and renal replacement therapy. Finally, a study of the 410 patients in EPIC II who had cirrhosis found a higher prevalence of infection (of which a greater proportion were abdominal), a higher frequency of MRSA infections, and a much higher hospital mortality rate (42% *v* 24% overall; 71% *v* 49% for septic shock).[64]

A point prevalence study of pediatric sepsis (SPROUT), similar to EPIC II, which focused on 128 sites in 26 countries, was published in 2015.[65] Of the 569 children with severe sepsis (8.2% prevalence in the pediatric intensive care unit population), the most common primary site of infection was the lungs (40%), followed by the bloodstream (19%), abdomen (8%), central nervous system (4%), and genitourinary system (4%). The most severe cases of sepsis had positive microbiology, including 28% Gram negative bacteria, 27% Gram positive bacteria, 13% fungi (12% candida), and 21% viruses. Nearly 75% required mechanical ventilation, and 45% were receiving corticosteroids. Hospital mortality was 25%, higher than previous estimates,[66] and thus more in line with recent studies in adults.[13]

Pathogenesis

Much is now known about how sepsis causes organ injury at a molecular, cellular, and organ level.

Organ and tissue level

As sepsis progresses from a localized infection to mild systemic inflammation and on to septic shock, the cardiovascular system undergoes major perturbations that are well known to intensive care practitioners. With the widespread use of pulmonary arterial catheters in the 1980s,[67] it became clear that after intravascular volume is restored, most patients with sepsis have a normal or raised cardiac output with low systemic vascular resistance. The preservation or enhancement in cardiac output occurs despite acute biventricular dysfunction that can last longer than a week.[68 69] Increased lactate in these patients predicts mortality.[70] This has traditionally been thought to reflect tissue hypoxia as a result of hypoperfusion,[71] a theory that stimulated much of the therapeutic focus during the past three decades on increasing systemic oxygen delivery in the setting of high-normal cardiac output.[72 73] Of note, alternative theories of sepsis induced hyperlactemia, such as aerobic glycolysis driven by enhanced adrenergic tone, have also been advanced.[74 75]

The endothelium can be thought of as an organ that covers an area of nearly 1000 m^2 and has important roles in regulating vasomotor tone, the movement of cells and nutrients into and out of tissues, the coagulation system, and the balance of inflammatory and anti-inflammatory signaling.[76] In sepsis, profound alterations to the endothelium occur, including increased leukocyte adhesion, a shift to a procoagulant state, vasodilation, and loss of barrier function, which all lead to widespread tissue edema.[77]

Microcirculatory alterations include an impaired response to local stimulation, as well as obstruction of microvessel lumens by microthrombi and plugs of white and red blood cells.[78 79] Widespread tissue factor expression, fibrin deposition, and impaired anticoagulant mechanisms (including activated protein C) can produce disseminated intravascular coagulation (DIC), a syndrome associated with increased organ dysfunction, bleeding (owing to consumption of platelets and clotting factors), and mortality.[80]

The endothelial changes in severe sepsis are associated with altered barrier function in other organs (fig 3). More permeable lung capillaries result in the accumulation of protein-rich edema fluid in the interstitial spaces of the lung, and in the presence of sepsis induced alveolar epithelial barrier dysfunction, the interstitial edema fluid floods into the alveoli. These changes result in perfusion-ventilation mismatch, arterial hypoxemia, and reduced lung compliance: ARDS.[81]

Combined breakdown of both the endothelial and epithelial barriers extends beyond the lung and is a key mechanism in widespread lethal organ dysfunction.[82] The gut epithelium becomes more permeable in the setting of hypercytokinemia.[83] This increased permeability sets in motion a vicious cycle of bacterial translocation, gut injury by luminal contents including activated pancreatic enzymes (autodigestion),[84] and worsening systemic inflammation that can perpetuate multiple organ dysfunction.[85] Indeed, in a prospective observational study of 47 critically ill patients in Canada, intestinal permeability independently predicted subsequent multiple organ dysfunction.[86] In the liver, sepsis impairs hepatocyte clearance of bilirubin (causing cholestasis) and many other crucial hepatic functions, including the transport and processing of enteric pathogen lipids,[87] further stimulating systemic inflammation.

Acute kidney injury (AKI) is common in severe sepsis and substantially increases the risk of death.[88] Although in the past septic AKI has been attributed to reduced renal perfusion and widespread tubular necrosis, little evidence supports the notion that either of these mechanisms are common or severe enough in sepsis to explain the profound degree of renal impairment.[89 90] Rather, septic AKI seems to involve more complex and subtle mechanisms of cytokine and immune mediated microvascular and tubular dysfunction.[91 92]

The nervous system is not simply an injured bystander in severe sepsis but an active participant in its early development, playing mostly an anti-inflammatory role. Carotid body chemoreceptors, vagal afferents, and brain areas with a constitutively permeable blood barrier respond to local and systemic cytokines, signaling to brainstem nuclei, which in turn send vagal, cholinergic efferents that inhibit inflammatory cytokine production by innate immune cells in the spleen, gut, and elsewhere.[93] Indeed, vagal nerve stimulation has been shown to attenuate cytokine signaling and endothelial injury in animal models of sepsis as well as shock from ischemia-reperfusion, burns, and pancreatitis.[94-97]

Encephalopathy is an early and common clinical finding in severe sepsis that can range from mildly impaired concentration to deep coma.[98] Delirium, as assessed by the confusion assessment method (CAM)-ICU method,

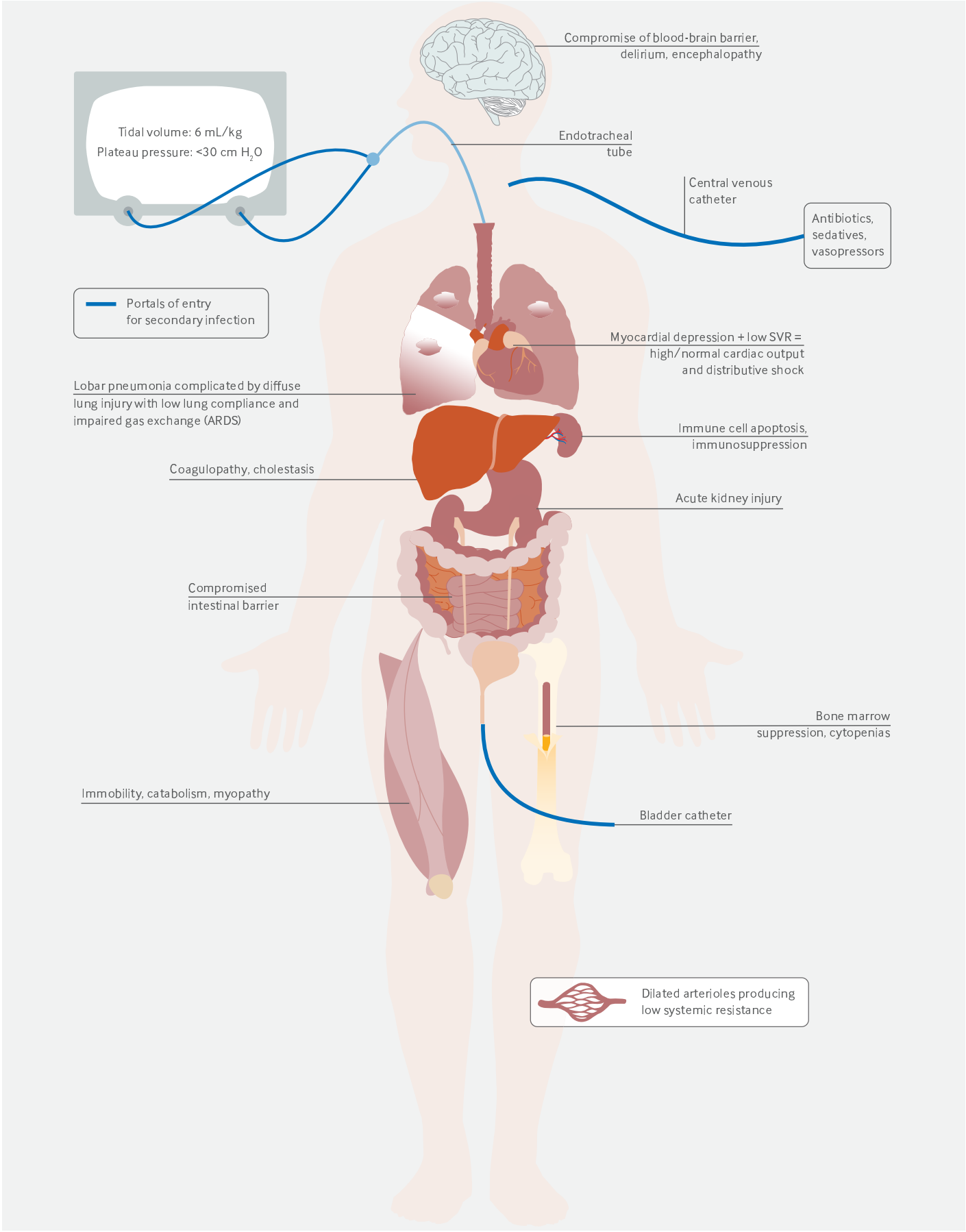

Fig 3| Organ failure in a critically ill patient with septic shock from pneumococcal pneumonia. ARDS=acute respiratory distress syndrome

is very common in ventilated patients,[99] and it is independently associated with mortality and long lasting neurocognitive deficits.[99 100] Infection can cause encephalopathy as a direct result of central nervous system infection, but more often it sets in motion a series of sterile events that perturb neurologic function. Systemic endothelial dysfunction compromises the blood-brain barrier, allowing inflammatory cytokines and cells to enter the brain, causing perivascular edema, oxidative stress, leukoencephalopathy, and widespread neurotransmitter alterations.[101 102] Coincident hepatic and renal dysfunction exacerbate toxin influx into the CNS. In addition, coagulopathy and impaired autoregulation of cerebral blood flow can together produce areas of ischemia and hemorrhage.[103] In a series of 23 patients with septic shock, ischemia and hemorrhage were detected at autopsy in 23 and six patients, respectively.[104]

Finally, the early proinflammatory state in severe sepsis often develops into a later and prolonged state of immune system dysfunction. Spleens harvested from ICU patients who had active sepsis when they died are largely depleted of $CD4^+$ and $CD8^+$ T cells, and the remaining splenocytes show marked reductions in stimulated cytokine production.[105] The loss of $CD4^+$ T cells seems to be mainly the result of apoptosis,[106] and it severely impedes the ability of these patients to mount an appropriate immune response to superimposed infections.[107] Indeed, multiple viruses (including cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and human herpesvirus 6) are often reactivated during the course of the illness, and cytomegalovirus viremia is predictive of fungal infection and 90 day mortality.[108] Similarly, lymphopenia four days after the diagnosis of sepsis is associated with secondary bacterial infection and predicts mortality at 28 days and one year.[109] Thus, it is not surprising that in prolonged sepsis there is a microbiologic trend towards subsequent infection with less virulent organisms.[110]

Septic organ dysfunction often perpetuates critical illness in a self reinforcing manner through several well defined pathways:

- ARDS often requires mechanical ventilation, which itself can further injure the lungs and enhance systemic inflammation[111]
- Sedatives needed to compel compliance with positive pressure ventilation can worsen septic associated encephalopathy and delirium,[112] leading to reduced mobility, worsened catabolism, and severe neuromuscular weakness
- Intestinal barrier dysfunction causes ongoing systemic translocation of pathogenic organisms and impaired nutritional status
- Immune system dysfunction leaves the host—who is commonly being treated with broad spectrum antibiotics and has portals for nosocomial infections (endotracheal tube, intravascular, bladder catheters)—highly susceptible to new infections with resistant bacteria and opportunistic organisms.

The combined effect of these self reinforcing processes (fig 3) explains much of the morbidity of severe sepsis (including the tendency to develop what has been termed "chronic critical illness"[113]). It has led to the increased emphasis on meticulous, evidenced based supportive critical care, which has probably helped improve outcomes in sepsis.

Cellular and molecular level

The molecular cascades unleashed by severe infection are complex, temporally dynamic, and at least partially dependent on the particular virulence factors of the invading pathogen.[114] A thorough description of infectious agents and inflammatory and cytokine signaling is beyond the scope of this review, and the reader is referred to more thorough reviews as indicated.

Here we summarize some key pathways and themes. One study synthesized and infused recombinant tumor necrosis factor α (TNF-α, a polypeptide originally named cachectin) into rats. Within three hours the animals developed tachypnea, lactic acidosis, and lethal shock, and they were found to have areas of ischemia and hemorrhage of the lungs, gut, kidneys, pancreas, and adrenal glands.[115] These effects closely resembled the known sequelae of high dose endotoxin administration,[116] thus showing that a single inflammatory macrophage derived cytokine can produce a clinical picture of septic shock. The same research group reported that infusing TNF-α blocking antibody fragments two hours before intravenous injection of *E coli* in anesthetized baboons prevented shock and organ failure.[117] Importantly, this therapeutic effect was lost if the antibody was infused any later than two hours before the bacteria, probably because of the rapid peak and decline of TNF-α signaling. This finding demonstrated the rapidly shifting cytokine milieu in serious infection, and it partly explains the failure of anti-TNF-α agents in the treatment of a heterogeneous population of patients with sepsis in the ICU.[118]

Inflammatory signaling

The innate immune system, composed mainly of macrophages, monocytes, granulocytes, natural killer cells, and dendritic cells, has evolved to detect pathogen associated molecular patterns (PAMPs; including components of bacterial, fungal, and viral pathogens such as endotoxin and β-glucan) and damage associated molecular patterns (DAMPS; endogenous molecules released from damaged host cells, including ATP, mitochondrial DNA, and high mobility group box 1 or HMGB1). DAMPs and PAMPs activate innate immune and some epithelial cells through pattern recognition receptors on the cell surface (toll-like receptors and C-type lectin receptors) or in the cytosol (NOD-like receptors, RIG-I-like receptors), initiating transcription of type I interferons and proinflammatory cytokines such as TNF-α, interleukin (IL)-1, and IL-6.[119 120] Some of these pattern recognition receptors (mostly NOD-like receptors) can assemble into molecular complexes termed inflammasomes, which are important in the maturation and secretion of the very potent cytokines IL-1β and IL-18, and can trigger highly inflammatory programmed cell death by caspase mediated rapid rupture of the plasma membrane, termed pyroptosis.[121] Proinflammatory cytokines in turn:

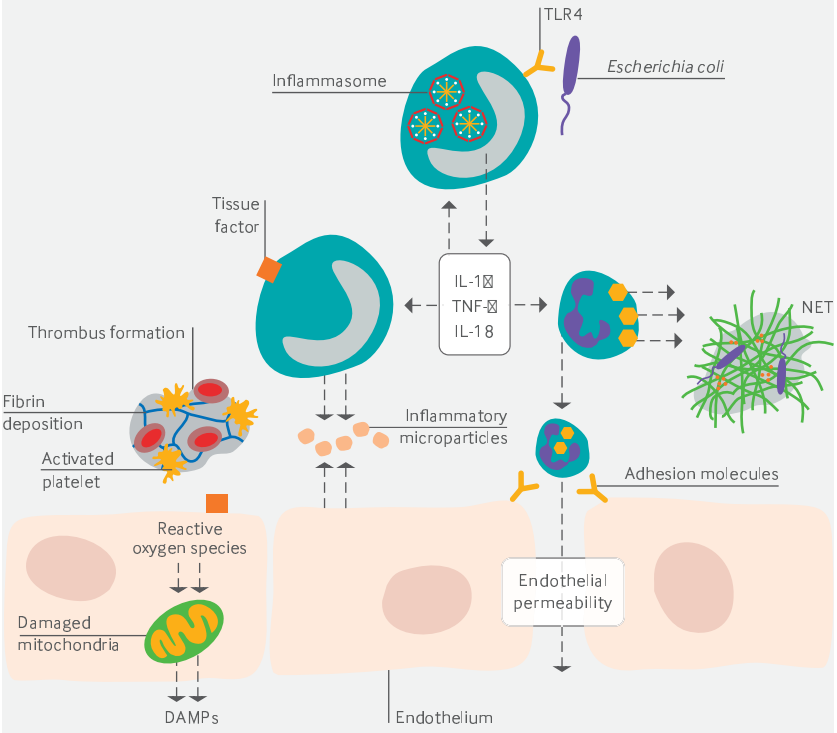

Fig 4| The self reinforcing pathophysiologic processes involved in sepsis. Endothelial injury results in activation of monocytes and granulocytes, endothelial barrier breakdown, immunothrombosis, and disseminated intravascular coagulation. DAMPs= damage associated molecular patterns; IL= interleukin; TLR4= Toll-like receptor 4; TNF-α=tumor necrosis factor α

- Increase the numbers, lifespan, and activation state of innate immune cells
- Increase adhesion molecule and chemokine expression by endothelial cells
- Induce many hepatic acute phase proteins such as complement and fibrinogen
- Cause neutrophils to release extracellular traps (NETs), web-like pro-coagulant collections of DNA and antimicrobial proteins and enzymes that form a scaffold for platelet activation[122]
- Cause the release (by activated platelets, endothelial cells, and leukocytes) of microparticles—vesicles that bud from the plasma membrane and contain inflammatory, pro-oxidant, and pro-coagulant lipids and proteins including tissue factor, angiopoietin-2, and von Willebrand factor multimers[123]
- Upregulate tissue factor expression by blood monocytes. In combination with the release of NETS and microparticles mentioned above, intravascular tissue factor expression results in "immunothrombosis,"[124] whereby microbes are trapped within thrombi that in turn attract and further activate leukocytes.

Early damage pathways

The inflammatory cytokine response is a highly evolutionarily conserved system that achieves rapid control of minor and localized infections. However, when the response exceeds a certain threshold systemic injury occurs:

- Reactive oxygen species (ROS) such as the hydroxyl radical and nitric oxide can damage cellular proteins, lipids, and DNA, and impair mitochondrial function
- Complement activation (especially C5a) further increases generation of ROS, granulocyte enzyme release, endothelial permeability, and tissue factor expression and may cause the death of adrenal medullary cells[125]
- Widespread immunothrombosis can result in DIC, with resultant impaired microvascular function and organ injury, along with further activation of inflammatory pathways

Thus at the molecular (fig 4) and tissue levels, sepsis is characterized by self reinforcing pathophysiologic processes.

Metabolic dysfunction

Even in the most severe, lethal septic shock and multiorgan failure, autopsy series show relatively little cell death outside of lymph tissues.[91] Mitochondrial proteins and DNA are damaged by high levels of ROS, and patients with sepsis have damaged and dysfunctional mitochondria.[91 126] Potentially exacerbated by the toxic effects of antibiotics on mitochondria, ATP levels drop, and to prevent a lethal drop in ATP cells may enter a state similar to hibernation.[127] A generalized reduction in energy expenditure at the cellular level is consistent with retained tissue oxygen tension in sepsis,[74] and this reduction probably exacerbates organ dysfunction as many viable cells reduce their performance of specialized functions. This leads to or exacerbates acute kidney injury, myocardial depression, hepatic dysfunction, encephalopathy, acute lung injury with increased lung endothelial and epithelial permeability to protein, and decreased barrier and transport functions of the gastrointestinal tract.[82]

Catabolism is another increasingly recognized characteristic of severe sepsis. A prospective study of 63 critically ill patients in England documented rapid and substantial loss of muscle mass, especially in patients with multiorgan failure.[128] Pain, corticosteroids, immobility, and inflammatory cytokines all contribute to the rapid breakdown of muscle tissue, liberating amino acids for gluconeogenesis to fuel the glucose dependent proliferation of innate immune cells.[129] Of note, the insulin insensitivity and hyperglycemia characteristic of sepsis and critical illness are proportional to the severity of the insult and may have evolved to ensure that glucose levels in the interstitial space (about 30% lower than in the blood) are adequate to support the massive immune response.[129]

Resolution pathways

Compensatory anti-inflammatory cytokine pathways are activated even in the first hours of severe sepsis. IL-10, produced by a variety of leukocytes, suppresses the production of IL-6 and interferon-γ, and stimulates the production of soluble TNF receptor and IL-1 receptor antagonist, helping to neutralize potent TNF-α and IL-1 signaling.[120] At the subcellular level, autophagy provides a way to eliminate DAMPs and PAMPs by packaging pathogens and damaged organelles and proteins in vesicles targeted for lysosomal degradation, reducing inflammasome activation.[130]

It has increasingly been recognized that resolution of inflammation after severe infection is not simply a passive process of the fading of inflammatory pathways, but instead involves a coordinated set of cell processes and newly recognized molecular signals. Once the pathogenic organisms have been eliminated from the host, damaged cells and infiltrating leukocytes must be cleared from the tissue. If the signaling milieu is favorable, these cells undergo apoptosis and are engulfed (mostly by macrophages), a process termed efferocytosis, triggering the release of the anti-inflammatory cytokines IL-10 and transforming growth factor β.[131] Recently discovered families of bioactive lipids termed lipoxins, resolvins, protectins, and maresins (also released during efferocytosis) have been shown to reduce ROS, endothelial permeability, and leukocyte recruitment, and further enhance macrophage efferocytosis.[132] Regulatory T cells (Tregs) and myeloid derived suppressor cells may also play important roles in the clearance of cytotoxic cells and production of anti-inflammatory cytokines.[131]

Treatment

The consistent improvements in survival after sepsis might suggest that a variety of proven, effective treatments had been implemented. However, there are still no approved specific molecular therapies for sepsis. Furthermore, controversy continues to surround nearly every variable in the management of sepsis, with consensus around only a few key points. Broadly speaking, attempts to normalize or enhance various aspects of the physiology of patients with sepsis (gas exchange, glucose control, oxygen delivery) have been either ineffective or harmful, emphasizing the value of large randomized trials to test what initially appear to be intuitively pleasing concepts in critically ill patients.

Early and effective antimicrobial treatment

In light of current practice, it is remarkable that as recently as the 1980s patients presenting to the emergency department with suspected bacterial meningitis had a median three hour delay in antibiotic administration, with 90% of the delay occurring after the initial encounter with the physician.[133] This delay was commonly caused by waiting for the lumbar puncture results, even when grossly cloudy cerebrospinal fluid was obtained; in community hospitals the delay was often lengthened by the practice of deferring to the admitting internist to order antibiotics after the patient arrived on the hospital ward.

A retrospective review of 2700 Canadian patients admitted with septic shock between 1989 and 2004 found that only 50% received effective antibiotics within six hours of the onset of hypotension.[134] Each hour of delay in antibiotic administration after the onset of shock was associated with a nearly 12% reduction in survival (odds ratio 1.12 per hour delay, 1.103 to 1.136). A more recent retrospective analysis in 2014 of 18 000 patients admitted to 165 ICUs with septic shock or severe sepsis also found that adjusted hospital mortality steadily increased as the delay in antibiotic administration increased (one hour: 25.9%, 24.5% to 27.2%; >6 hours: 33.1%, 30.9% to 35.3%).[135]

A meta-analysis in 2015 of 11 studies failed to show increased mortality in patients receiving antibiotics more than one hour (odds ratio 1.46, 0.89 to 2.40) or three hours (1.16, 0.92 to 1.46) after the recognition of severe sepsis or septic shock.[136] However, this study has been criticized for excluding many eligible trials, thereby increasing the chances of signal dilution and bias.[137] The most recent guidelines from the Surviving Sepsis Campaign (SSC) recommend administration of effective intravenous antibiotics within an hour of recognizing severe sepsis or septic shock.[138] Although the precise temporal benefits of antibiotics may be controversial (and unknowable given that a randomized trial would be unethical), there is consensus that effective antibiotics should be given as soon as possible. To meet this goal, hospitals have implemented a variety of screening procedures and protocols to help identify patients with severe sepsis early, rapidly obtain microbiologic samples, and administer broad spectrum antibiotics.

Resuscitation

Although early prospective randomized trials suggested that boosting oxygen delivery improved outcomes, there were methodological problems.[139] One prospective study of nine patients with sepsis and nine without in whom care was being withdrawn suggested that the oxygen delivery threshold for anaerobic metabolism was similar in patients with and without sepsis (3.8 (standard deviation 1.5) *v* 4.5 (1.3) mL/min/kg; P>0.28) and that it was much lower than suspected.[75] In the mid-1990s, two important trials in heterogeneous populations of critically ill patients targeted either a high mixed venous oxygen saturation or a supranormal cardiac output, finding that so called goal oriented therapy either did not affect survival or significantly reduced it (fig 5).[72 140]

As enthusiasm waned for increasing oxygen delivery to patients with sepsis, an influential single center study was published in 2001 (fig 5) that randomized a more homogeneous group of 263 patients with SIRS and hypotension (or lactate of at least 4 mmol/L) within one to two hours of admission to the emergency department to one of two protocols for six hours.[73] Standard therapy targeted central venous pressure of 8-12 mm Hg, mean arterial pressure of 65-90 mm Hg, and urine output of 0.5 mL/kg/h using crystalloid or colloid infusions and vasopressors. "Early goal directed therapy" (EGDT) targeted the same three parameters as well as a central venous oxygen saturation of 70% using red blood cell transfusions and inotropes as needed. The EGDT group had a 16% absolute improvement in in-hospital mortality (47% *v* 31%; relative risk 0.58, 0.38 to 0.87). On the basis of this trial, the EGDT protocol was widely adopted (including a grade 1C recommendation from the SSC[138]) and many centers began using specialized catheters to monitor central venous oxygen saturation continuously.

Although outcomes improved with so called sepsis bundles,[150] controversy persisted over whether the resource intensive EGDT protocol was itself effective or instead helped create the systems to recognize sepsis earlier and improve other aspects of care, such as the speed of antibiotic administration. In the past two years, three

Date/ Study (ref)	Intervention	Population,* setting	Primary outcome	Result	Comments
1994[72]	**Hemodynamic management** Dobutamine (2-200 µg/kg/min) to achieve cardiac index 4.5 L/min/m², DO_2 600 mL/min/m², VO_2 >170 mL/min/m²	• 100 mixed sepsis, ARDS • 2 ICUs	In-hospital mortality	**Harm** 34% *v* 54%; P=0.04	Same trend for harm in ARDS and septic shock subgroups
1995[140]	**Hemodynamic management** Three groups: 1. Control: normal cardiac index (2.5-3.5 L/min/m²) 2. Supranormal cardiac index (>4.5) 3. Normal SvO_2 (>70%)	• 762 mixed sepsis, ARDS, hemorrhage • 56 ICUs	ICU mortality	**No differences** **Group 2** *v* **1:** RR 1.01 (0.71-1.43) **Group 3** *v* **1:** RR 1.16 (0.82 to 1.64)	Similar results regardless of subgroup including sepsis, septic shock Many intensivists abandoned strategy of targeting supranormal DO_2
2001 EGDT (Rivers trial)[73]	**Early goal directed therapy** EGDT algorithm† for 6 hours initiated in the ED compared with standard therapy	• 263 severe sepsis • 1 ED	In-hospital mortality	**Benefit** RR 0.58 (0.38 to 0.87)	Required continuous monitoring of $ScvO_2$ Highly influential study, protocols adopted into guidelines
2011 FEAST[141]	**Fluid resuscitation** Three groups: 1. No bolus fluids 2. Bolus 5% albumin 3. Bolus 0.9% saline	• 3141 children with severe febrile illness§ • Hospitals in Uganda, Kenya, Tanzania	48 hour mortality	**Harm** **Group 2** *v* **1:** RR 1.45 (1.10 to 1.92); **Group 3** *v* **1:** RR 1.44 (1.09 to 1.90)	Similar results at 4 weeks Recruiting hospitals lacked intensive care facilities No subgroup showed benefit from fluid resuscitation
2012 6S Trial[142]	**Type of fluid for resuscitation** 6% hydroxyethyl starch *v* Ringer's acetate (control)	• 804 severe sepsis • 26 Scandinavian ICUs	Death or dialysis dependence at 90 days	**Harm** **Death:** RR 1.17 (1.01 to 1.36) Dialysis: RR 1.35 (1.01 to 1.80)	
2014 ProCESS[143]	**Management of early septic shock** Three groups: 1. Usual care 2. EGDT 3. Protocol based standard therapy‡	• 1341 septic shock • 31 North American EDs	60 day mortality	**No differences** **Group 2** *v* **3:** RR 1.15 (0.88-1.51); **Group 3** *v* **1:** RR 1.04 (0.82-1.31)	Severity of illness similar to original EGDT trial
2014 ARISE[144]	**Management of early septic shock** Usual care *v* EGDT	• 1600 septic shock • 51 EDs Australia/New Zealand	90 day mortality	**No differences** AD -0.3% (-4.1% to 3.6%)	
2014 ALBIOS[145]	**Type of fluid for resuscitation** 20% albumin and crystalloid *v* crystalloid (control)	• 1818 severe sepsis • 100 Italian ICUs	28 day mortality	**No differences** RR 1.00 (0.87 to 1.14)	
2014 SEPSISPAM[146]	**Blood pressure target (mm Hg)** MAP 80-85 *v* 65-70 (control)	• 776 septic shock • 29 French ICUs	28 day mortality	**No differences** HR 1.07 (0.84 to 1.38)	Higher MAP group with more atrial fibrillation, less dialysis (in those with chronic hypertension)
2014 TRISS[147]	**Hemoglobin target** Transfusion threshold of 70 *v* 90 g/L	• 1005 septic shock • 32 Scandanavian ICUs	90 day mortality	**No differences** 70 *v* 90 g/L: RR 0.94 (0.78 to 1.09)	No difference in ischemic events
2015 ProMISe[148]	**Management of early septic shock** EGDT *v* Usual care	• 1260 septic shock • 56 English EDs	90 day mortality	**No differences** RR 1.01 (0.85 to 1.20)	EGDT increased costs
2015 SPLIT[149]	**Type of fluid for resuscitation** Buffered crystalloid *v* saline	• Patients requiring crystalloid • 4 New Zealand ICUs	AKI within 90 days	**No differences** RR 1.04 (0.80 to 1.36)	Patients low risk for outcome, modest fluid administration

*The least sick population included (for example, "severe sepsis" implies both severe sepsis and septic shock.)
†See text for protocol description.
‡Fluids and vasopressors were used to achieve heart rate and blood pressure goals, central line optional, hemoglobin target 75 g/L;
§Complicated by prostration/coma, respiratory distress, or both, and impaired perfusion (based on physical examination findings).
Abbreviations: AD=absolute risk difference; AKI=acute kidney injury; ARDS=acute respiratory distress syndrome; DO_2=oxygen delivery; ED=emergency department; EGDT=early goal directed therapy; HR=hazard ratio; ICU=intensive care unit; MAP= mean arterial pressure; RR=relative risk (numbers in parenthesis are 95% confidence intervals); $ScvO_2$=central venous oxygen saturation; SvO_2=mixed venous oxygen saturation; VO_2=oxygen consumption.

Fig 5| Selected randomized fluid and vasopressor resuscitation trials in sepsis and critical illness[72-149]

large multicenter randomized controlled trials (RCTs) from the US (ProCESS[143]), the UK (ProMISe[148]), and Australia and Asia (ARISE[144]) have been published (>4200 patients in total) that each compared the EGDT protocol with usual care (fig 5). These three studies all found that EGDT did not significantly affect survival, indicating that other improvements in sepsis and critical care explain the improved outcomes.

Uncertainties still exist regarding the optimal type of fluid, the optimal volume, and the best way to monitor the response to therapy.

Fluid type

Level I evidence suggests that starches should be avoided,[142] and that albumin is not clearly beneficial relative to crystalloid (fig 5).[145 151] A prospective open label pilot study of 1533 ICU patients during a control period followed by a six month period of restricted use of high chloride fluids (normal saline, 4% albumin) suggested that high chloride fluids may cause acute kidney injury (odds ratio for AKI during restricted period 0.52, 0.37 to 0.75).[152] Although a recent double blind RCT of 2278 ICU patients in New Zealand reported no reduction in AKI with buffered crystalloid compared with saline (fig 5), the population was low to moderate risk for this outcome and exposure to the study fluid was modest (mean about 2 L).[149]

Resuscitation volume

It is widely considered standard of care to administer several liters of fluid in severe sepsis and septic shock (as was the case in all patients in the three recent large trials). No high quality RCT evidence exists to support this practice, and a single randomized study of critically ill children

in resource poor settings lacking advanced therapies for pulmonary edema questioned its safety.[141] Nonetheless, it remains expert opinion that the decrease in septic shock mortality over the past several decades reflects in part the benefits of early fluid resuscitation.

Resuscitation adequacy

Over the past several decades many ICU physicians have moved away from the assessment of static cardiac filling pressures and towards dynamic indices of physiology. These include ultrasound assessments of central venous volume and left ventricular function,[153] although it is worth reiterating that the evidence basis for trying to augment cardiac output in patients with sepsis is weak. Furthermore, excessive fluid administration in the setting of a more permeable endothelium can exacerbate organ dysfunction, including the development of acute respiratory failure from ARDS.[154] In addition, multiple investigators have shown that positive fluid balance in these patients is an independent risk factor for death.[155 156]

Lactate clearance was popularized by a 2010 study in 300 patients with sepsis that showed non-inferiority to EGDT,[157] and although not used in the recent three large negative trials of EGDT, many practitioners continue to measure serial lactate values to inform resuscitation targets. The optimal systemic blood pressure is also unknown, with a recent study reporting that targeting a mean arterial pressure of 80-85 mm Hg compared with 60-65 mm Hg modestly improved renal function, although rates of atrial fibrillation were increased and no difference in survival was seen (fig 5).[146]

Timing and choice of vasopressors

It is unclear when vasopressors should be started during the resuscitation of septic shock. Most practitioners give at least 2-3 L crystalloid or colloid to adults before starting a vasopressor. Although some advocate giving more fluid in an attempt to avoid the use of vasopressors, it is worth noting that vasopressors also constrict the large venous capacitance vessels and thus augment cardiac preload in addition to afterload.[158 159] Although limited by its retrospective design and reliance on complex statistical methods, a recent evaluation of the interaction between fluid and vasopressor administration in nearly 3000 patients with septic shock found that mortality was lowest when vasopressors were started one to six hours after onset and when at least 1 L of fluid was given during the first hour.[160]

A 2011 systematic review of 23 randomized trials of patients with shock found no convincing evidence for the superiority of one vasopressor over another.[161] However, an influential meta-analysis from 2012 reported a higher mortality associated with dopamine than with norepinephrine (noradrenaline).[162] Accordingly, the most recent SSC guidelines recommend norepinephrine as first line agent, epinephrine (adrenaline) or low dose vasopressin as second line agents, and the avoidance of dopamine and phenylephrine as empiric vasopressor therapy.[138]

Transfusion threshold

ProCESS, ProMISe, and ARISE suggested that a strategy of increasing oxygen delivery with red blood cell transfusions as part of EGDT did not improve survival. The recent TRISS study that randomized nearly 1000 patients with septic shock in 32 Scandinavian ICUs to a transfusion threshold of 70 or 90 g/L hemoglobin found no difference in 90 day mortality or the rate of ischemic events (fig 5).[147]

Other supportive care

Improvements in general critical care have played a major role in improving outcomes in sepsis.

Lung protective ventilation

In 2000, low tidal volume ventilation in patients with ARDS was shown to have a marked survival benefit,[163] with an absolute reduction in hospital mortality of 8.9%. A subsequent analysis showed that this benefit extended to patients with sepsis who had ARDS.[164] The adoption of low tidal volume, lung protective ventilation in patients with sepsis and ARDS has been a major factor in the improvement in outcomes over the past 15 years.

Restrictive fluid therapy once initial resuscitation is accomplished

In a trial of 1000 patients with ARDS randomized to a conservative or liberal fluid management strategy (once out of shock), the conservatively managed patients had a better oxygenation index and higher number of ventilator-free days (14.6 (0.5) *v* 12.1 (0.5); P<0.001).[154] Notably, there were trends towards improved survival (25.5% *v* 28.4%, P=0.3) and less dialysis within 60 days in the conservatively managed patients (10% *v* 14%; P=0.06).

Use of sedatives

With the recognition that the excessive use of sedatives is probably harmful,[165-167] many hospitals have now implemented protocols to reduce unnecessary sedation. Awake patients are more capable of rehabilitation, and the early mobilization of critically ill patients improves delirium and functional outcomes as well as reducing the duration of mechanical ventilation.[168]

Catheters and tubes

Rates of ventilator associated pneumonia have decreased, partly because of the engineering of endotracheal tubes to decrease biofilm formation and microaspiration,[169] as well as improved oral hygiene.[170] Improvements in intravascular catheter design, placement technique, maintenance, and timely removal have reduced nosocomial infections,[171 172] as have criteria for the removal of unnecessary urinary catheters.[173]

Nutrition and glucose management

Despite these advances, several questions remain regarding the optimal supportive care of patients with sepsis. The proper timing and intensity of nutritional support remains unclear. There is some weak older evidence for reduced infectious complications with enteral feeding,[174] but recent randomized trials report no benefit with more aggressive enteral or parenteral nutritional supplementation.[175 176] These results have led the SSC to recommend enteral feedings as tolerated.[138] Patients with sepsis are often hyperglycemic, yet the optimal glucose target is

unknown. Notably, targeting a glucose of 80-110 mg/dL (1mg/dL=0.06mmol/L), compared with <180 mg/dL, in a mixed population of 6104 critically ill patients has been shown to increase 90 day mortality (odds ratio 1.14, 1.02 to 1.28),[177] and the SSC now recommends insulin therapy to maintain glucose <180 mg/dL.[138]

Additional uncertainties

Other uncertainties include the optimal sedative regimen and the timing and dose of renal replacement therapy,[178-180] with current guidelines recommending either continuous or intermittent dialysis to help manage fluid balance in patients with septic shock.[138]

Molecular targeted sepsis therapies

The seminal preclinical TNF-α experiments from the 1980s (see above) generated enthusiasm for the hypothesis that blocking proinflammatory cytokine cascades in sepsis would reduce mortality. However, a subsequent clinical trial in patients with septic shock showed that treatment with anti-TNF antibodies increased mortality.[118] Similarly, corticosteroids were reported as early as 1976 to reduce mortality in septic shock dramatically,[181] yet after dozens of subsequent trials, there is still no consensus about efficacy.[182] This pattern of promising preclinical and early clinical results followed by disappointing large phase III and IV trials has been repeated dozens of times in the past four decades for drugs targeting a variety of cytokine pathways, bacterial virulence factors, and the coagulation cascade (fig 6).[198]

Reasons for failure and possible remedies

Much has been written about the reasons that most targeted molecular therapies have been unsuccessful in patients,[198 199] and a few key points are worth emphasizing here. Beyond the standard challenges of optimizing pharmacokinetics and length of treatment, sepsis research has been confronted by other serious difficulties.

Patient heterogeneity

Some researchers have argued that the definition of sepsis using broad clinical criteria results in so much heterogeneity that therapies effective for a "generic" patient with sepsis may be impossible to find.[200] Others have argued that severe sepsis and septic shock may represent distinct disease phenotypes that occur independently rather than on a continuum.[7] But even when clinical criteria are narrowed, challenges remain. Recruiting patients into clinical trials is arduous and time intensive. Although TNF was shown in preclinical models to rise and fall quickly at the beginning of sepsis, the clinical trial with etanercept (that demonstrated harm) enrolled patients at varying times after the onset of sepsis. Even when patients are recruited within a narrow window after admission their presentation may have been delayed, so the true onset of infection is often unknowable. Temporal heterogeneity is a formidable obstacle in trials of anti-inflammatory agents in sepsis because patients tend to progress from a state of inflammatory cytokines into a state of immunosuppression: agents that might be helpful early in a patient's course could be harmful later.

Heterogeneity also derives from biological variability related to the patient's:

- Age
- Sex
- Comorbidities including liver and kidney disease and underlying cancer
- Diet and substance misuse, including exposure to cigarette smoke
- Genetics
- Site of infection (especially intravascular *v* extravascular)[201]
- The pathogen that is causing the sepsis.

Imagine a trial of a novel therapeutic approach to treating confirmed Gram negative septic shock for patients admitted within six hours, a seemingly narrow slice of sepsis. It is likely that large baseline differences in innumerable biological processes would obscure a modest or even strong therapeutic signal for survival if the following patients were compared in the study:

- A 19 year old female athlete who became ill two hours earlier with meningococcal sepsis
- An 80 year old man with dementia and longstanding urinary retention, *E coli* bacteremia, and aspiration pneumonia complicated by ARDS
- A 60 year old man with diverticulitis and an associated abscess but no bacteremia.

Strategies to reduce heterogeneity include limiting enrollment on the basis of the above list of criteria or using biomarkers to help enrich for the targeted underlying pathophysiology. These approaches could be aided by more thorough analyses of failed phase III trials (although data are often still held by the drug companies[202]) to identify subgroups of patients who appeared to derive benefit. Although these kinds of strategies have been used (for example, IL-6 levels to stratify patients in an anti-TNF trial,[184]fig 6) and are probably necessary, they increase the costs of research and reduce the generalizability of the results.

Multiple pathways to injury

In a remarkable study in which low dose intravenous endotoxin was given to volunteers (a seemingly modest stimulus), thousands of genes in leukocytes were found to undergo large temporally dynamic changes,[203] and more recent work has shown similar complexity in the changes of small molecule metabolites.[204] As outlined in detail above, the molecular cascades and organ dysfunction that often accompany sepsis are parallel and often self reinforcing. Thus, even when patient heterogeneity is reduced and pathophysiology is conserved, it may be naive to expect that blocking one among hundreds of pathways will be sufficient to produce a measurable clinical improvement. Furthermore, gains from blocking one pathway may be more than offset by unintended consequences. For example, reducing neutrophil recruitment and activation may attenuate injury from inflammation at the expense of reduced bacterial killing and wider dissemination of infection.

Possible solutions include identifying and targeting the key proximal regulatory pathways that orchestrate subsequent responses, or alternatively (given the obvi-

Agent/Study (ref)	Rationale/intervention	Population*	Primary outcome	Result	Comments
ANTI-CYTOKINES					
Etanercept[118]	Escalating doses of a fusion protein of Fc and extracellular domain of TNF receptor that neutralizes the potent inflammatory cytokine TNF	141 septic shock	28 day mortality	**Harm** Significant dose response† for mortality (P=0.02)	No measurement of TNF-α in the enrolled patients Drug now licensed for a variety of autoimmune diseases
Afelimomab[184]	Monoclonal antibody fragments against TNF-α Stratified by IL-6 level at enrollment	2634 severe sepsis stratified by IL-6	28 day mortality	**Mild improvement in patients with raised IL-6** OR 0.74 (0.56 to 0.99)	Subsequent 2013 meta-analysis of 15 trials[183] suggested possible modest benefit with antibody (rather than fusion protein) strategies, estimated definitive trial would require 10 000 patients
Anakinra[186]	Recombinant IL-1ra, a monocyte/macrophage protein that specifically inhibits the potent inflammatory cytokine IL-1	696 severe sepsis	28 day mortality	**No improvement** 36.4% placebo *v* 33.1% anakinra (P=0.36)	Initiated after a phase III study of 893 less sick patients showed a trend towards improved mortality[185]
ANTI-VIRULENCE FACTORS					
HA-1A CHESS[187]	Monoclonal antibody against the lipid A portion of LPS	2199 septic shock	14 day mortality	**No improvement** RR 1.08 (0.97 to 1.21)	Same results when the analysis was confined to the 621 patients with Gram negative bacteremia
E5[188]	Monoclonal antibody against a broad range of Gram negative endotoxins	1090 severe sepsis	14 day mortality	**No improvement** 29.7% E5 *v* 31.1% placebo (P=0.67)	Enrollment limited to documented or probable Gram negative infection (e.g. feculent peritonitis)
Eritoran ACCESS[189]	Lipid A-like molecule that blocks LPS binding to TLR4	1961 severe sepsis	28 day mortality	**No improvement** HR 1.05 (0.88 to 1.26)	
AGENTS TARGETING COAGULOPATHY					
Activated protein C (drotrecogin alfa) PROWESS[190]	Promotes fibrinolysis and inhibits thrombosis (may improve microcirculatory disruptions)	1690 severe sepsis	28 day mortality	**Benefit** ARR 6.1% (1.9% to 10.4%) RR 0.8 (0.69 to 0.94)	Only drug successfully licensed for sepsis Partially adopted into clinical practice but remained controversial: serious bleeding events, ethical concerns about incorporation into guidelines for sepsis bundles[191]
Activated protein C PROWESS-SHOCK[192]	Subgroup analysis from PROWESS suggested greater benefit among sickest patients In part undertaken to answer ongoing questions about benefits and risks	1697 septic shock	28 day mortality	**No improvement** RR 1.09 (0.92 to 1.28)	Drug withdrawn from the market after publication
Antithrombin III KyberSept[194]	Levels decline rapidly in early sepsis	2314 severe sepsis	28 day mortality	**No improvement** RR 1.01 (0.91 to 1.11)	Increased bleeding in patients also receiving heparin RR 1.77 (1.43-2.18) A subsequent meta-analysis suggested no benefit and increased bleeding (regardless of concurrent anticoagulation)[193]
Heparin HETRASE[195]	500 units/hour for 7 days	319 sepsis	Length of stay, organ dysfunction	**No improvement** For hospital mortality: OR 0.85 (0.42 to 1.93)	
IMMUNE STIMULATION					
G-CSF (filgrastim)[196]	Enhances neutrophil production and function	701 severe sepsis and bacterial pneumonia	28 day mortality	**No improvement** 25.5% placebo *v* 29.0% G-CSF (P=0.383)	
GM-CSF (sargramostim)[197]	Promotes survival, proliferation, and bacterial phagocytosis by neutrophils and monocytes/macrophages	38 severe sepsis and immunosuppression	Immunologic	Improved mHLA-DR expression and stimulated cytokine production	Reduced expression of mHLA-DR was both a study entry criterion (low levels associated with immune cell dysfunction) and outcome measure Phase III study ongoing (fig **7**)

*The least sick population included (for example "severe sepsis" implies both severe sepsis and septic shock).
†As assessed by the Cochran-Mantel-Haenszel test.
Abbreviations: LPS=lipopolysaccharide; TLR4=toll-like receptor 4; IL-6=interleukin-6; IL-1ra=interleukin-1 receptor antagonist; ARR=absolute risk reduction; GM-CSF=granulocyte-macrophage colony

Fig 6| Selected randomized pharmacologic trials in sepsis[118-197]

ous practical challenges of delivering therapeutics early enough to accomplish this) intervening in multiple downstream pathways simultaneously. Thus, trials involving combinations of therapies may be needed. Also, point of care testing that would allow better phenotyping of the patient's clinical and biological profile could select patients more optimally for trials of new therapeutics, an approach that was recently evaluated in patients with ARDS.[205]

Limitations of preclinical models

The most commonly used murine models of sepsis include endotoxin administration, cecal ligation and puncture, and exogenously administered pathogenic bacteria. Almost without exception inbred, young healthy animals are studied, and typically no advanced monitoring is used and minimal or no supportive care is given (antibiotics, respiratory support including supplemental oxygen, fluid and vasopressor resuscitation, renal replacement therapy). Beyond these obvious differences from the composition and care of patients with sepsis, important species differences probably explain many of the discrepancies between preclinical successes and clinical trial failures in drug development. For example, mice are notoriously resistant to endotoxin (a sterile and thus artificial insult), requiring orders of magnitude higher doses than are needed in humans to cause illness.

An influential study published in 2013 compared the response of transcriptional networks of circulating mouse and human leukocytes to burns, endotoxin, and trauma.[206] After finding little correlation between human and murine responses, the authors argued provocatively that translational research should shift away from mouse models. However, several important limitations of this study were highlighted in a recent review that makes a strong case for enhancing the relevance of murine models (rather than abandoning them) by including the use of outbred strains of different ages and shifting away from endotoxin models towards bacterial infections of the lungs, urinary tract, and abdomen.[207] Other appealing approaches include the use of larger animal models (such as sheep) with the inclusion of at least some forms of supportive care, recognizing that most patients no longer die of the acute inflammatory response but of subsequent organ failure.[208]

Emerging treatments

Several large phase III and IV clinical trials are currently under way (fig 7). In light of the substantial improvements in sepsis outcomes with advances in supportive critical care, the current trials seek to further optimize fluid, hemodynamic, and sedative management. After many failures of strategies seeking to decrease the inflammatory cascades in early sepsis, the focus of immunomodulatory research has shifted to attempts to boost immunity during the later phase of immunoparalysis.

Recognizing that multiple organ failure is responsible for much of the clinical burden of sepsis, early stage research has increasingly focused on strategies to enhance endothelial and epithelial barrier function,[211] bioenergetics,[127] and active inflammation resolution pathways.[212] One promising approach is the use of cell based therapies such as allogeneic mesenchymal stem or stromal cells, which have potent immunomodulatory, antimicrobial, bioenergetic, and barrier enhancing effects.[213] These cells are currently being tested in phase II trials for ARDS[214] and in a Canadian phase I trial in sepsis (NCT02421484).

As the science evolves, we are likely to develop novel therapeutic strategies that optimize the host's response to infection. Simultaneously we must redouble efforts worldwide at more effectively deploying proven infection prevention measures, including access to safe drinking water and sanitation, public health system surveillance and outreach, vector control, and vaccination.[215]

Guidelines and the new sepsis definitions

The SSC was formed in 2002 as a collaboration of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. The SSC published its first guidelines in 2004.[216] These guidelines made graded recommendations regarding diagnostics, antibiotics, fluid and vasopressor resuscitation, mechanical ventilation, sedation, and the use of drotrecogin alfa (activated protein C; fig 6). Critics noted that the SSC derived 90% of its initial funding from Eli Lilly (maker of drotrecogin alfa), and that established therapies such as antibiotics and fluids received lower ratings (owing to lack of RCT evidence) than did drotrecogin alfa.[191] In 2005, the SSC began publishing highly influential quality indicators (sepsis bundles) based on their guidelines, which included many components of the EGDT approach,[73] including measurement of central venous oxygen saturation in septic shock. The SSC has since divested itself of industry support and has periodically updated its guidelines, most recently in 2013.[138] After the publication of ProCESS, ARISE, and ProMISe, the SSC released a brief update to its guidelines in April of 2015 (http://www.survivingsepsis.org/SiteCollectionDocuments/SSC_Bundle.pdf), which puts less emphasis than EGDT does on achieving specific hemodynamic goals.

In February 2016, a new consensus definition and clinical criteria for sepsis were issued by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine.[3] Building on previous iterations of consensus definitions, the new Sepsis-3 definitions eliminate the SIRS category and put more emphasis on scoring organ dysfunction. Additionally, a new clinical sepsis screening tool was proposed to identify patients with sepsis outside of the ICU. Developed using logistic regression on established datasets and termed quick SOFA, this score still awaits prospective validation in diverse clinical settings.[217] The screen is positive if two out of the following are true—respiratory rate >22, Glasgow coma score <15, systolic blood pressure <100 mm Hg.[3]

Notably, the syndromes of sepsis and septic shock as newly defined in Sepsis-3 remain broad categorizations that do not separate patients on the basis of pathophysiologic mechanisms. Whether this revised set of diagnostic criteria will improve clinical trial design or the clinical care of patients remains to be determined.

Registry/Trial/ Completion date	Sites	Agent/intervention	Phase	To enroll*	Primary outcome	Rationale
IMMUNE STIMULATION						
NCT-02361528 GRID 2018	France	GM-CSF (sargramostim)	III	488 severe sepsis with reduced mHLA-DR	ICU acquired infection	Improve immunoparalysis
NCT-01649921 2016	Netherlands	IFN-γ	III	20 septic shock	Stimulated cytokine production	Improve immunoparalysis
COAGULOPATHY						
NCT-01598831 2018	International	Thrombomodulin (ART-123)	III	800 severe sepsis + coagulopathy (INR >1.40)	28 day mortality	Sepsis associated downregulation of endothelial thrombomodulin related to coagulation activation; also with immunomodulatory functions[209]
GLUCOCORTICOIDS						
NCT-01448109 ADRENAL 2016	Australia and New Zealand	Hydrocortisone (200 mg daily for 7 days)	IV	3800 septic shock	90 day mortality	Large trial of low dose steroids hopes to resolve a longstanding area of controversy
SUPPORTIVE: RESUSCITATION						
NCT-02508649 SEPSIS-ACT 2018	Belgium, Denmark, France	Selepressin (vasopressin type 1a receptor agonist)	II/III	1800 septic shock	Vasopressor and ventilator-free days	Similar to vasopressin but with favorable profile on endothelial permeability
NCT-02454348 NOVEL 2018	US	Vasopressin and norepinephrine *v* norepinephrine alone	IV	418 septic shock	90 day mortality	Previous data support use of vasopressin as add-on therapy
ISRCTN-20769191 VANISH 2015	UK	2x2: Vasopressin *v* norepinephrine as initial vasopressor and IV hydrocortisone *v* placebo	IV	412 septic shock	Renal failure-free days through 28 days	Vasopressin may be more effective if used earlier and may prevent kidney injury
ISRCTN-12776039 LeoPARDS 2016	UK	Levosimendan *v* placebo for 24 hours	IV	516 septic shock	Organ dysfunction (mean SOFA score)	Sensitizes myocardium to calcium without increasing oxygen demand, anti-inflammatory Earlier data showed improved microcirculatory flow, hepatic and renal function
NCT-01797978 2017	South Korea	Methylene blue	III	354 septic shock	28 day mortality	Improves blood pressure in vasopressor refractory shock Enrollment dependent on need for high dose vasopressors (norepinephrine >0.2 μg/kg/min)
NCT-02079402 CLASSIC 2015	Scandanavia	Conservative *v* liberal fluid resuscitation when shock persists after 30 mL/kg crystalloid	IV	150 septic shock	Resuscitation volume	Targets patients after the initial 6 hours of resuscitation Conservative group with trigger guided fluid boluses rather than hemodynamic guided
NCT-02369900 2019	US	Esmolol titrated to heart rate 80-94 beats/min	II	104 septic shock	Need for vasopressor support at 6 hours	Recent single center trial reported improved survival[210] Patients must require norepinephrine at least 0.1 μg/kg/min
SUPPORTIVE: OTHER						
NCT-01455116 CASS 2016	Denmark	Mild induced hypothermia (32-34°C)	II/III	560 severe sepsis, intubated	30 day mortality	Reduce organ metabolism, microcirculatory thrombosis, bacterial growth
NCT-02317549 SSAIL 2017	US and Canada	Enteral tranexemic acid	II	260 septic shock	Days free of MV, vasopressors, and RRT	Preserves gut integrity by inhibiting digestive enzymes and "autodigestion"
NCT-01046669 EUPHRATES 2017	US and Canada	Extracorporeal treatment of blood with polystyrene composite covalently bonded to polymyxin B	III	650 septic shock with endo-toxemia	28 day mortality	Adsorption of endotoxins
NCT-02389036 SuDDICU 2019	International	Selective decontamination of the digestive tract with antibiotics	III	24,000 mech-anically ventilated	Hospital mortality	Some prior evidence for efficacy but concerns about promotion of antibiotic resistance have limited use Trial not limited to patients with sepsis
NCT-01739933 MENDSII 2018	US	Dexmedetomidine *v* propofol	III	530 severe sepsis	Days free of delirium or coma	Earlier trials suggested propofol or dexmedetomidine were superior to benzodiazepines
NCT-02378545 2015	UK	Oxygen (non-rebreather at 15 L/min v target oxygen saturation of 94%)	IV	300 sepsis	90 day mortality	Rationale exists for both harm and benefit from hyperoxia

*The least sick population included (for example, "severe sepsis" implies both severe sepsis and septic shock).

Abbreviations: GM-CSF=granulocyte-macrophage colony stimulating factor; ICU=intensive care unit; IFN-γ=interferon γ; INR=international normalized ratio; IV=intravenous; mHLA-DR=monocytic human leukocyte antigen-DR; MV=mechanical ventilation; NIH=National Institutes of Health; RRT=renal replacement therapy; SOFA=sequential organ failure assessment.

Fig 7| Selected ongoing randomized trials in sepsis from the NIH clinical trials registry and international standard randomized controlled trials number (ISRCTN) database[209 210]

QUESTIONS FOR FUTURE RESEARCH

- What is the optimal fluid and vasopressor resuscitation strategy in the early phase of septic shock?
- Will lung protective ventilation in patients with sepsis reduce the development of acute respiratory distress syndrome?
- Will new treatments reduce the incidence of acute kidney injury in patients with sepsis?
- Can rapid, inexpensive, and specific microbiologic tests for defining causative pathogens be developed using genetic and other approaches?
- Will we develop new effective and safe antibiotics in an era of increasingly common drug resistant pathogens?
- How does the microbiome change in sepsis and how might this be leveraged therapeutically?
- What are the long term physical, cognitive, and psychosocial changes in patients who survive sepsis, and can we develop effective rehabilitative techniques?
- Can we improve the ability of preclinical models of sepsis to predict therapeutic efficacy?
- Can we develop a range of point-of-care biomarkers to group patients with sepsis into pathophysiologic categories? This would improve our understanding of the biology and may enhance clinical trial design
- How will the recently released definitions and clinical criteria for sepsis[3] shape its clinical detection, treatment, and research?

Conclusions

The study of the impact, pathogenesis, and treatment of sepsis has generated important new insights at every level of analysis. Sepsis remains a common, expensive, and deadly problem throughout the world. It is a complicated and dynamic condition that resists one size fits all approaches. However, despite the failure of many therapeutics in clinical trials, sepsis outcomes have improved substantially with major improvements in supportive care, including rapid recognition of sepsis and delivery of effective antibiotics, resuscitation with fluid therapy in early septic shock, lung protective ventilation, more judicious use of fluid therapy once shock has resolved, better guidelines for blood product transfusion, and enhanced methods to reduce secondary nosocomial infections. Novel therapeutic pathways targeting organ dysfunction hold renewed promise for both septic and sterile inflammation, but thoughtful preclinical approaches will be essential going forward. In addition, to reduce heterogeneity and enhance the prospects of therapeutic efficacy for new treatment strategies, the use of clinical and biological criteria to select and phenotype patients with sepsis for clinical trials will need to be improved.

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