

Septic shock

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Septic shock, the most severe complication of sepsis, is a deadly disease. In recent years, exciting advances have been made in the understanding of its pathophysiology and treatment. Pathogens, via their microbial-associated molecular patterns, trigger sequential intracellular events in immune cells, epithelium, endothelium, and the neuroendocrine system. Proinflammatory mediators that contribute to eradication of invading microorganisms are produced, and anti-inflammatory mediators control this response. The inflammatory response leads to damage to host tissue, and the anti-inflammatory response causes leucocyte reprogramming and changes in immune status. The time-window for interventions is short, and treatment must promptly control the source of infection and restore haemodynamic homoeostasis. Further research is needed to establish which fluids and vasopressors are best. Some patients with septic shock might benefit from drugs such as corticosteroids or activated protein C. Other therapeutic strategies are under investigation, including those that target late proinflammatory mediators, endothelium, or the neuroendocrine system.

In 1879–80, Louis Pasteur showed for the first time that bacteria were present in blood from patients with puerperal septicaemia. One woman survived, leading Pasteur to state that “Natura medicatrix won the victory”, an opinion consistent with the notion that sepsis is a systemic response to fight off pathogens (panel, figure 1). However, a consensus on the definition of sepsis was reached only a decade ago,¹ and the list of symptoms was updated very recently.² Sepsis is now defined as infection with evidence of systemic inflammation, consisting of two or more of the following: increased or decreased temperature or leucocyte count, tachycardia, and rapid breathing. Septic shock is sepsis with hypotension that persists after resuscitation with intravenous fluid. Normally, the immune and neuroendocrine systems tightly control the local inflammatory process to eradicate invading pathogens. When this local control mechanism fails, systemic inflammation occurs, converting the infection to sepsis, severe sepsis, or septic shock.

Epidemiology

The yearly incidence of sepsis is 50–95 cases per 100 000, and has been increasing by 9% each year.³ This disease accounts for 2% of hospital admissions; roughly 9% of patients with sepsis progress to severe sepsis, and 3% of those with severe sepsis experience septic shock,⁴ which accounts for 10% of admissions to intensive care units.⁵

The occurrence of septic shock peaks in the sixth decade of life.⁵ Factors that can predispose people to septic shock include cancer, immunodeficiency, chronic organ failure, iatrogenic factors,^{3,5,6} and genetic factors,⁷ such as being male,⁸ non-white ethnic origin in North Americans,³ and polymorphisms in genes that regulate immunity.⁹

Cause

Infections of the chest, abdomen, genitourinary system, and primary bloodstream cause more than 80% of cases of sepsis.^{3,5,6} Rates of pneumonia, bacteraemia, and

multiple-site infection have increased steadily over time, whereas abdominal infections have remained unchanged and genitourinary infections have decreased.^{3,5}

The occurrence of gram-negative sepsis has diminished over the years to 25–30% in 2000. Gram-positive and polymicrobial infections accounted for 30–50% and 25% of cases, respectively (table 1).^{3,5,6} The fact that multidrug-resistant bacteria and fungi now cause about 25% of cases is cause for concern.^{5,6} Viruses and parasites are identified in 2–4% of cases, but their frequency could be underestimated.⁵ Lastly, cultures are negative in about 30% of cases, mainly in patients with community-acquired sepsis who are treated with antibiotics before admission.

Pathomechanisms

The definition of sepsis is often over-simplified as being the result of exacerbated inflammatory responses. However, pathogenesis involves several factors that interact in a long chain of events from pathogen recognition to overwhelming of host responses.

Search strategy and selection criteria

We attempted to identify all relevant studies irrespective of language or publication status (published, unpublished, in press, and in progress). We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 1, 2004) using the terms “sepsis” and “septic shock”, and MEDLINE (1966 to June 2004), EMBASE (1974 to June 2004), and LILACS (www.bireme.br; accessed Aug 1, 2003) databases using the terms “septic shock”, “sepsis”, “septicaemia”, “endotoxin”, “lipopolysaccharide” variably combined with “incidence”, “prevalence”, “cause”, “origin”, “diagnosis”, “management”, “treatment”, “therapy”, “prognosis”, “morbidity”, and “mortality”. Studies were selected on the basis of relevance to septic shock.

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Panel: Key dates in sepsis research

- Prognostic discrimination between localised and systemic infections and recognition of fever as a major symptom (Hippocrates, 4th century BCE)
- Description of inflammation: rubor et tumor cum calore et dolore (Celsus, 1st century CE, Galen, 2nd century CE)
- Death of Lucrezia Borgia from puerperal septicaemia (1519)
- Surgery proposed to avoid microbial dissemination from infected wounds (Paré, 16th century)
- Antiseptic methods proposed to avoid puerperal septicaemia (Semmelweis, 1841-47)
- Introduction of the term “microbes” (Sédillot, 1878)
- Identification of microbes in blood from patients with sepsis (Pasteur, 1879-80)
- Description of phagocytosis as a host response against microbes (Metchnikoff, 1882)
- Role of bacterial toxins described (Roux and Yersin, 1888)
- Concept of endotoxin-induced shock and death (Pfeiffer, 1894)
- Reproduction of infection by auto-inoculation of blood from patients (Mocutkosky, 1900)
- First antibody to endotoxin (Besredka, 1906)
- Discovery of penicillin (Fleming, 1929)
- First biochemical characterisation of endotoxin (Boivin and Mesrobian, 1933)
- Description of stress syndrome (Selye, 1936)
- Dawn of intensive care medicine (Hamburger, Lassen, 1953)
- Description of mechanisms underlying endotoxin shock (Hinshaw, 1956-58)
- Role of tumour necrosis factor α in endotoxin-induced shock (Beutler and Cerami, 1985)
- Genetic predisposition to infection (Sorensen, 1988)
- Current definitions of sepsis (Bone, 1989)
- First genomic polymorphism associated with severity of sepsis (Stüber, 1996)

Patterns and receptors

Matzinger¹⁰ redefined immunity by postulating that immune system activity stemmed from recognition of and reaction to internal danger signals, rather than from discrimination between self and non-self molecules. Danger signals also include recognition of exogenous molecules, pathogen-associated molecular patterns, which are surface molecules such as endotoxin (lipopolysaccharide), lipoproteins, outer-membrane proteins, flagellin, fimbriae, peptidoglycan, peptidoglycan-associated lipoprotein, and lipoteichoic acid; and internal motifs released during bacterial lysis, such as heat-shock proteins and DNA fragments. These molecules are common to pathogenic, non-pathogenic, and commensal bacteria, making “microbial-associated molecular patterns” a better term. These patterns are recognised by specific pattern recognition receptors, which induce cytokine expression. These microbial patterns act synergistically with one another, with host mediators, and with hypoxia.

Of pattern recognition receptors, the toll-like receptors are characterised by an extracellular leucine-rich repeat domain and a cytoplasmic toll-interleukin-1 receptor (TIR) domain that shares considerable homology with the interleukin-1 receptor cytoplasmic domain. Currently, ten toll-like receptors have been described in humans, and the list of their specific microbial ligands is growing.¹¹ Signal transduction after interaction between microbial-associated molecular patterns and these receptors results in activation of numerous adaptors, some with the TIR domain (myeloid differentiation protein [MyD] 88, TIR domain-containing adaptor protein, TIR receptor domain-containing adaptor protein inducing interferon β [TRIF], and TRIF-related adaptor molecule), and of kinase proteins. MyD88 interacts directly with most toll-like receptors and appears upstream from activation of the transcription nuclear factor- κ B. TRIF results in activation of nuclear factor interferon regulatory factor 3, promoting production of interferon β (figure 2).¹¹ Additionally, molecules in the cytoplasm (MyD88s, interleukin-1 receptor-associated kinase-M, Tollip, suppressor of cytokine signalling 1) or at the cell surface (single immunoglobulin interleukin-1R-related molecule, ST2) negatively control the signalling cascade.

Nod1 and Nod2 proteins are intracellular pattern recognition receptors.¹² Nod1's ligand is a peptidoglycan fragment that is almost exclusive to gram-negative bacteria. Nod2 detects a different such fragment and also recognises muramyl dipeptide, the smallest bioactive fragment common to all peptidoglycans. Four peptidoglycan recognition proteins (PGRPs), a third family of pattern recognition receptors, have been characterised in people.¹³ Three are membrane-bound proteins, PGRP-I α , PGRP-I β , and PGRP-L. The fourth is the soluble molecule PGRP-S.

	Estimated frequency*
Gram-positive bacteria	30–50%
Meticillin-susceptible <i>S aureus</i>	14–24%
Meticillin-resistant <i>S aureus</i>	5–11%
Other <i>Staphylococcus</i> spp	1–3%
<i>Streptococcus pneumoniae</i>	9–12%
Other <i>Streptococcus</i> spp	6–11%
<i>Enterococcus</i> spp	3–13%
Anaerobes	1–2%
Other gram-positive bacteria	1–5%
Gram-negative bacteria	25–30%
<i>E coli</i>	9–27%
<i>Pseudomonas aeruginosa</i>	8–15%
<i>Klebsiella pneumoniae</i>	2–7%
Other <i>Enterobacter</i> spp	6–16%
<i>Haemophilus influenzae</i>	2–10%
Anaerobes	3–7%
Other gram-negative bacteria	3–12%
Fungus	
<i>Candida albicans</i>	1–3%
Other <i>Candida</i> spp	1–2%
Yeast	1%
Parasites	1–3%
Viruses	2–4%

*From published clinical trials^{45,150} and epidemiological studies.^{5,6}

Table 1: Main pathogens in septic shock

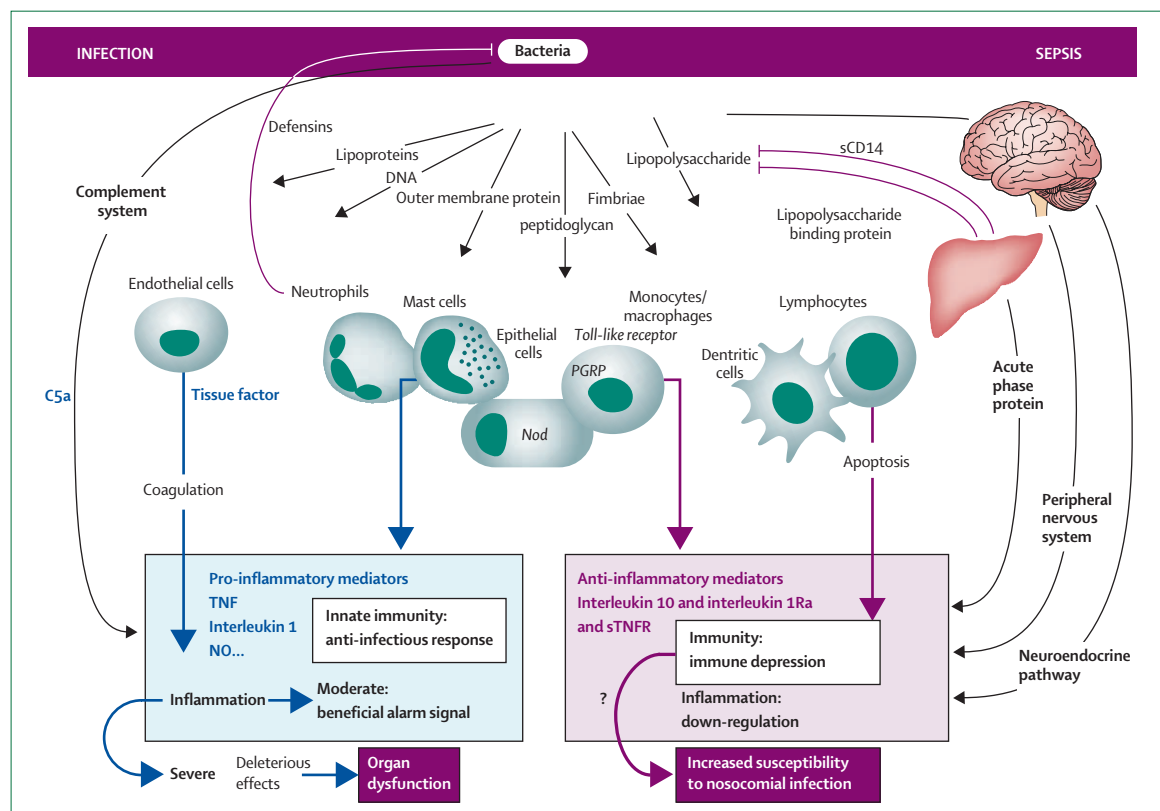


Figure 1: From bacteria to disease
Barred lines=inhibition. Arrows=activation or consequences.

Leucocytes

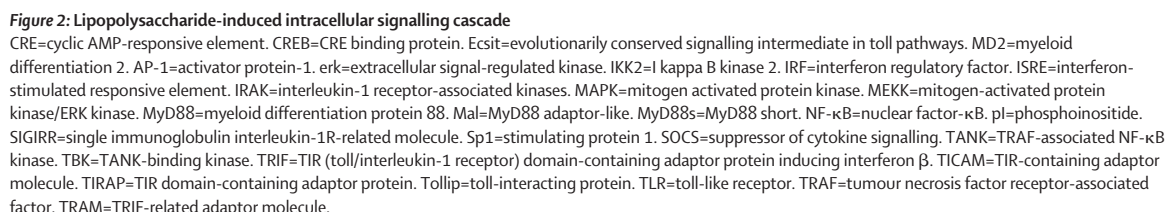
Sepsis is associated with migration of activated leucocytes from the bloodstream to inflammatory tissues,¹⁴ and with intensified bone-marrow production of leucocytes that are released into the blood as newly differentiated or immature cells. Profound changes arise in peripheral-blood lymphocytes^{15,16} and monocytes,¹⁷ as well as changes in cell surface markers (eg, chemokine CXCR2, tumour necrosis factor [TNF] receptor p50 and p75, interleukin 1R, C5a receptor, and toll-like receptors 2 and 4). Down-regulation of HLA DR expression on monocytes followed lipopolysaccharide challenge in healthy volunteers,¹⁸ and in patients with sepsis is mediated by interleukin 10¹⁹ and cortisol,²⁰ and is correlated with death.²¹

Leucocytes release numerous proteases that play a pivotal part in combating infections. For example, compared with controls, mice that have a knockout of the neutrophil-elastase gene are more susceptible to sepsis and death after intraperitoneal gram-negative, but not gram-positive, infection.²² In people, concentrations of elastase are increased in plasma and bronchoalveolar lavage fluid,²³ and might contribute to shock and organ dysfunction, as suggested by experiments using elastase inhibitor²⁴ or mice that have

a knockout of an enzyme required for protease maturation²⁵ or a natural protease inhibitor²⁶.

Cell apoptosis in patients with sepsis varies across cell types. It is increased for blood and spleen lymphocytes and spleen dendritic cells, unchanged for spleen macrophages and circulating monocytes, and reduced for blood neutrophils and alveolar macrophages.²⁷ Apoptosis is also abnormal in the thymic, intestinal, and pulmonary epithelia and in the brain, but not in the endothelium. In animals, glucocorticoids,²⁸ Fas ligand,²⁹ and TNF³⁰ are the main proapoptotic factors, and caspase inhibitors or overexpression of B-cell lymphoma/leukaemia-2, prevent sepsis-induced apoptosis and death.²⁷ In people, the mechanisms and role of apoptosis in the pathogenesis of septic shock remain unclear.

Ex-vivo experiments with blood cells from patients have shown blunted cytokine production in response to mitogens with lymphocytes³¹ (both T-helper 1 and T helper 2 cytokines),³² and in response to lipopolysaccharide with neutrophils^{33,34} and monocytes.³⁵ Neutrophils and monocytes from endotoxin-challenged healthy volunteers gave similar results.^{36,37} Although interleukin 10 might partly account for sepsis-associated monocyte hyporesponsiveness to lipopolysaccharide,³⁸ the underlying molecular mechanisms remain to be clarified. Synthesis of TNF induced by lipopolysaccha-



septic patients. However, by contrast with the cell response to lipopolysaccharide, production of TNF after stimulation with heat-killed *Staphylococcus aureus*, *Escherichia coli*, or muramyl dipeptide was unaltered (unpublished data), suggesting diversified leucocyte responsiveness to microbial agonists.⁴⁰ Thus, we propose the term leucocyte reprogramming, the clinical relevance of which remains to be explored.

In mice, bacteria-mediated epithelial-cell apoptosis could contribute to immune defences via activation of the Fas/Fas ligand system.⁴⁴ However, lipopolysaccharide might alter the epithelial tight junctions in the lung, liver, and gut, thereby promoting bacterial translocation and organ failure.⁴⁵ Nitric oxide, TNF, interferon γ , and high mobility group box 1 (HMGB1) contribute to the functional disruption of epithelial tight junctions.⁴⁶ Underlying mechanisms might include an inducible NO synthase-associated decrease in expression

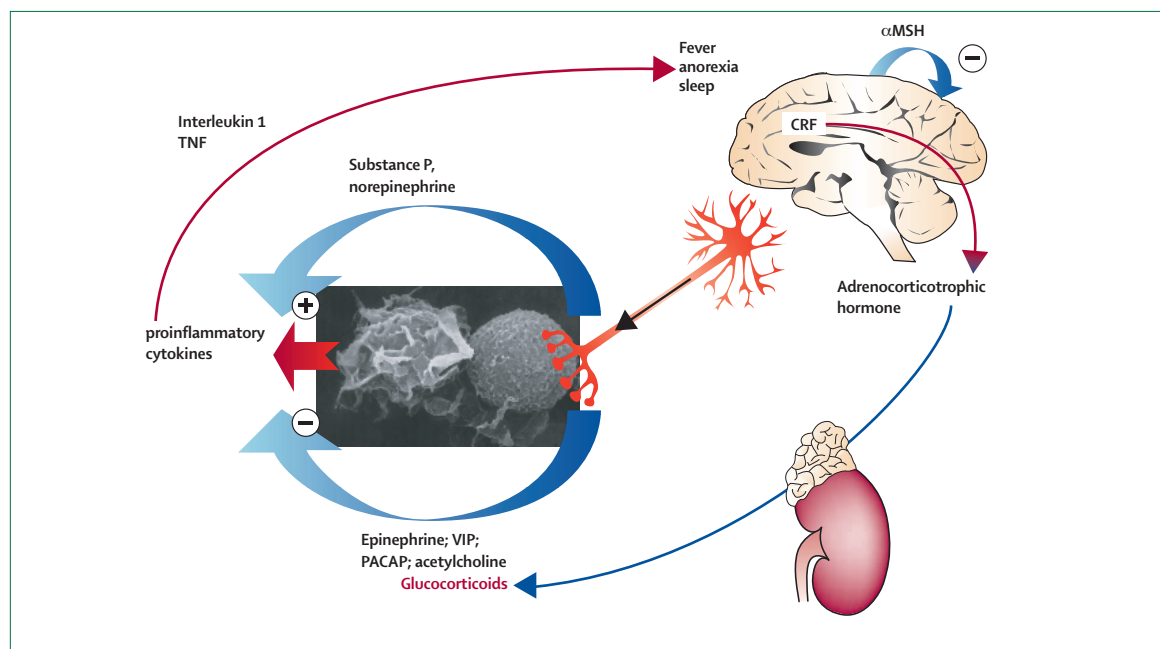


Figure 3: Crosstalk between immune, neurological, and endocrine systems

Proinflammatory cytokines initiate neuroendocrine loop, leading to production of glucocorticoids, and their own production is affected by different neuromediators. CRF=corticotropin releasing factor. PACAP=pituitary adenylate cyclase activating peptide. VIP=vasoactive intestinal polypeptide. MSH=melanocyte stimulating hormone.

of the tight junction protein zonula occludens 1, as well as internalisation of the apical junctional complex transmembrane proteins called junction adhesion molecule 1, occludin, and claudin-1/4.⁴⁷

Endothelium

Endothelial cells between blood and tissues promote adhesion of leucocytes, which can then migrate into tissues. On the one hand, experiments with knockout

mice⁴⁸ or animals treated with adhesion molecule-specific antibodies⁴⁹ suggest that adhesion molecules expressed on leucocytes or endothelial cells (ie, lymphocyte function associated antigen 1, intercellular adhesion molecule 1, endothelial leucocyte adhesion molecule 1, L-selectin, and P-selectin) might contribute to tissue damage. On the other hand, other adhesion-molecule blockade worsened cardiovascular and metabolic functions.⁵⁰ In patients with sepsis,

Disorders		Putative consequences
Cortisol	Impaired synthesis, circadian rhythm Impaired clearance from plasma Impaired transport to tissues Peripheral tissue resistance	Impaired contractile response to α -agonists: contributes to shock Inflammation Organ dysfunction Death
Renin and aldosterone	Shift of aldosterone from renin dependency to adrenocorticotropin dependency with hyper-reninaemia and hypoaldosteronism	Salt loss and hypovolaemia contribute to shock
DHEA, DHEAS	Usually decreased levels—mechanisms unknown?	Unknown
Sex hormones	Androstenedione and oestrogen concentrations are raised. Concentrations of testosterone, luteinising hormone, and follicle stimulating hormone are decreased. Loss of pulsatile secretion of gonadic hormones	Unknown
Thyroid hormones	Loss of pulsatile secretion of thyrotropin, reduced secretion of thyroid stimulating hormone and thyroid hormone secretion, and altered peripheral thyroid hormone metabolism (changes in tissue deiodinase activities), resulting in low circulating T_3 and high rT_3 concentrations and decreased T_4 concentrations	Possibly contribute to muscle protein loss and malnutrition
Vasopressin	Neuronal apoptosis triggered by inducible NO synthase, resulting in impaired vasopressin synthesis and release, mainly in late phase of septic shock	Contributes to shock
Insulin	Cytokines impair transcription of glucose transporter 4 gene and mediate systemic insulin resistance, resulting in hyperglycaemia and high concentrations of circulating insulin	Enhances immune cell and neurone functions. Hyperglycaemia promotes superinfection and polyneuropathy, and increases the risk of death
Growth hormones	Loss of pulsatile secretion	Possibly contributes to lean body mass loss and malnutrition

DHEA=dehydroepiandrosterone. DHEAS=dehydroepiandrosterone sulphate.

Table 2: Summary of endocrine disorders during septic shock

Systemic inflammatory response syndrome	Two or more of the following: <ul style="list-style-type: none"> ● Body temperature >38.5°C or <35.0°C ● Heart rate >90 beats per minute ● Respiratory rate >20 breaths per minute or arterial CO₂ tension <32 mm Hg or need for mechanical ventilation ● White blood cell count >12 000/mm³ or <4000/mm³ or immature forms >10%
Sepsis	Systemic inflammatory response syndrome and documented infection (culture or gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism; or focus of infection identified by visual inspection—eg, ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge)
Severe sepsis	Sepsis and at least one sign of organ hypoperfusion or organ dysfunction: <ul style="list-style-type: none"> ● Areas of mottled skin ● Capillary refilling time ≥3 s ● Urinary output <0.5 mL/kg for at least 1 h or renal replacement therapy ● Lactates >2 mmol/L ● Abrupt change in mental status or abnormal electroencephalogram ● Platelet counts <100 000/mL or disseminated intravascular coagulation ● Acute lung injury—acute respiratory distress syndrome ● Cardiac dysfunction (echocardiography)
Septic shock	Severe sepsis and one of: <ul style="list-style-type: none"> ● Systemic mean blood pressure <60 mm Hg (<80 mm Hg if previous hypertension) after 20–30 mL/kg starch or 40–60 mL/kg serum saline, or pulmonary capillary wedge pressure between 12 and 20 mm Hg ● Need for dopamine >5 µg/kg per min or norepinephrine or epinephrine <0.25 µg/kg per min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)
Refractory septic shock	Need for dopamine >15 µg/kg per min or norepinephrine or epinephrine >0.25 µg/kg per min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)

Table 3: Definitions of diseases

neutrophils showed an $\alpha 4$ -integrin-dependent increase in the capacity for vascular cellular adhesion molecule 1 binding.⁵¹ The therapeutic effect of modulation of leucocyte adhesion to the endothelium remains unexplored in people.

Endotoxin and cytokines induce tissue factor expression by monocytes and endothelial cells in healthy volunteers challenged with lipopolysaccharide⁵² and in patients with sepsis.⁵³ In animals, protective effects from administration of tissue factor pathway inhibitor or antibodies to tissue factor or from factor VIIa inhibition suggest a link between inflammation and coagulation. In people, no protective effects from administration of this inhibitor have been reported.⁵⁴ Coagulation might aggravate inflammation, especially after interaction of the endothelium with thrombin and factor Xa. In a peritonitis model, blockade of coagulation was harmful.⁵⁵ However, in heterozygous protein-C-deficient mice, disseminated intravascular coagulation was worsened by injection of lipopolysaccharide,⁵⁶ and, in people, reduction of the concentrations of protein C was associated with down-regulation of coagulation.⁵⁷

Proinflammatory mediators

During the past 15 years, convincing evidence that cytokines protect against infection came from experiments with recombinant proinflammatory cytokines—particularly TNF, interleukin 1, and

interferon γ —and antibodies to cytokines and with mice that had a knockout for a single cytokine or its receptor. Similar approaches to investigate toxic shock or infection conclusively showed lethal effects of TNF, interleukin 1 β , interleukin 12, interleukin 18, interferon γ , granulocyte-macrophage colony-stimulating factor, macrophage migration inhibitory factor, interferon β , and HMGB1. In people, cytokines are produced in excess and are therefore detectable in blood, where they are normally absent.⁵⁸ However, the circulating cytokines are merely the tip of the iceberg,⁵⁹ and cell-associated cytokines can be identified even when amounts in plasma are undetectable.³⁵

Sepsis is associated with increased concentrations of histamine in plasma from mast cells or basophils (or both) after activation of complement pathways with upregulation of anaphylatoxins C3a and C5a.⁶⁰ Whereas exogenous histamine or selective histamine H2 receptor agonists protect against endotoxin shock,^{61,62} anaphylatoxins enhance vascular permeability and smooth muscle contraction, and are chemoattractants for leucocytes. Moreover, compared with wildtype mice, C5-deficient mice responded to lipopolysaccharide with reduced concentrations of TNF and a lower severity index, and antibodies to C5a or C5a receptors prevented death from sepsis.⁶³ By contrast, mice with a knockout for C4, C3, and C3 receptor were more susceptible to endotoxin, and C1 inhibitor protected against death from sepsis.⁶⁴

Proinflammatory cytokines induce synthesis of phospholipase A2, inducible cyclo-oxygenase, 5-lipoxygenase, and acetyltransferase, which contribute to synthesis of eicosanoids (prostaglandins and leukotrienes) and platelet-activating factor. These factors, acting through specific G-protein-coupled receptors, promote inflammation, altering vasomotor tone and increasing blood flow and vascular permeability. Mice which are deficient in phospholipase A2 receptor⁶⁵ and inducible cyclo-oxygenase, but not those deficient in 5-lipoxygenase, are resistant to endotoxin. However, prostaglandins E2 can also reduce production of TNF.

Superoxide anion, which is produced by NADPH oxidase, oxidises and alters proteins and unsaturated fatty acids of phospholipids. However, some oxidised phospholipids can prevent endotoxin-induced inflammation by blocking the interaction between lipopolysaccharide and lipopolysaccharide-binding protein and CD14.⁶⁶ Mice that had a knockout for NADPH oxidase compounds were more susceptible to severe infections than mice that did not, although their sensitivity to endotoxin remained unaltered.⁶⁷

Mice deficient in inducible NO synthase merely exhibit less severe hypotension after lethal endotoxin challenge.⁶⁷ In people, large amounts of NO are released after endotoxin exposure or cytokine-related stimulation of inducible NO synthase activity in inflamed tissues⁶⁸ and vessel walls.⁶⁹ This NO excess contributes to

development of microvessel damage, vascular hyporeactivity, and organ dysfunction, probably by induction of apoptosis.⁶⁹

Anti-inflammatory mediators

Anti-inflammatory cytokines and soluble receptors are produced in large amounts during sepsis. They downregulate production of proinflammatory cytokines and protect animals from sepsis and endotoxin-induced shock. These effects are evident for interleukin 10 (although the effects of this cytokine vary with time, dose, and site of expression), for transforming growth factor β , interferon α , and interleukin 4, interleukin 6, and interleukin 13. On the one hand, interleukin 6 induces a broad array of acute-phase proteins that limit inflammation, such as α -1-acid-glycoprotein or C-reactive protein. More recently, interleukin-1 receptor antagonist, lipopolysaccharide binding protein, and soluble CD14 were identified as acute-phase proteins. On the other hand, interleukin 6 could induce myocardial depression during meningococcal septicaemia.⁷⁰ Though large amounts of circulating interleukin-1 receptor antagonist and soluble receptors for TNF have been reported in sepsis, it remains unclear whether these levels are sufficient to counteract proinflammatory cytokines.⁵⁸

Neuromediators have a major role in control of inflammation (figure 3). Substance P increases cytokine production, histamine release via basophil and mast-cell degranulation, leucocyte adhesion and chemotaxis, and vascular permeability. Catecholamines interfere with cytokine production in diverse ways. Norepinephrine, via the α_2 -adrenergic receptor, increases TNF production,⁷¹ whereas epinephrine interaction with the β_2 -adrenergic receptor decreases such production *in vitro*⁷² and *in vivo* in lipopolysaccharide-challenged healthy volunteers, and also enhances production of interleukin 10.⁷³ Furthermore, epinephrine increases production of interleukin 8⁷⁴ and suppresses production of NO.⁷⁵ The anti-inflammatory effects of β -agonists are mediated through reduced degradation of I κ B α ⁷⁶ and through increased intracellular concentrations of cyclic AMP. Vasoactive intestinal peptide and pituitary adenylate cyclase-activating peptide are two anti-inflammatory neuropeptides that inhibit cytokine production and protect mice from lipopolysaccharide lethality.^{77,78} In rats treated with lipopolysaccharide, vagal nerve stimulation attenuated hypotension and reduced concentrations of TNF in plasma and liver⁷⁹ through interaction between acetylcholine and the $\alpha 7$ subunit of the nicotinic receptor at the macrophage surface.⁸⁰ Finally, α -melanocyte stimulating hormone, another neuromediator expressed in the brain, could lessen inflammation by inhibition of proinflammatory cytokine production.⁸¹

Cross-talk between cytokines and neurohormones is the cornerstone of restoration of homeostasis during stress.⁸² Production and release of vasopressin and

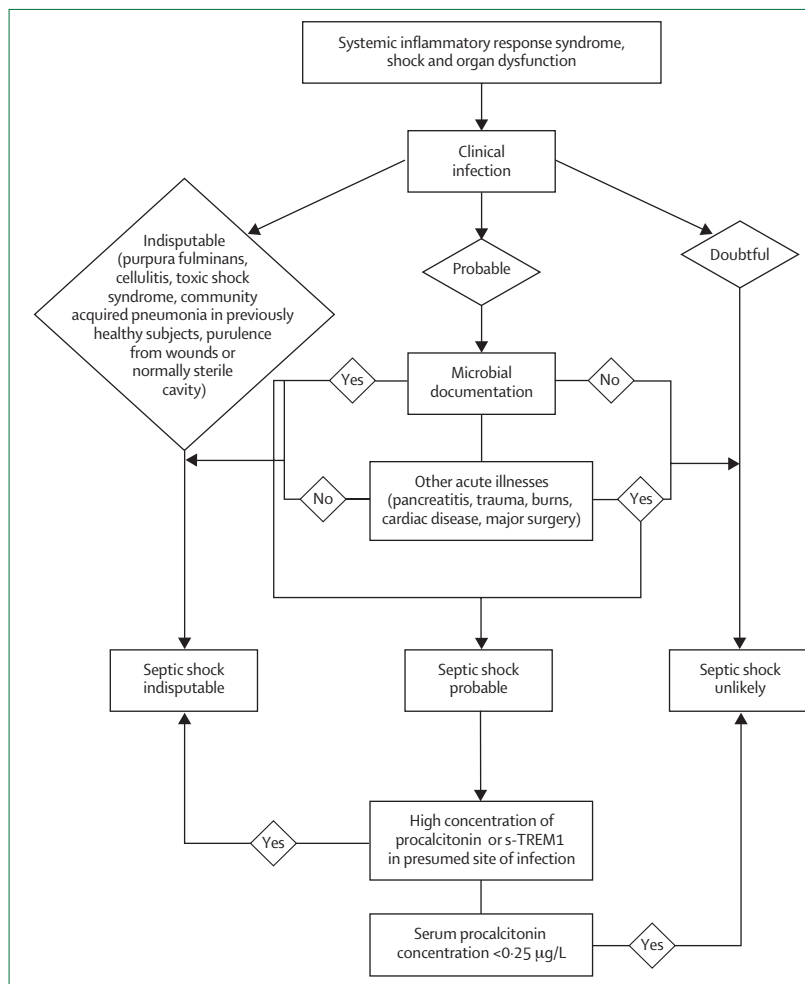


Figure 4: Decision tree for diagnosis of septic shock

corticotropin-releasing hormone are enhanced by circulating TNF and interleukin 1, interleukin 6, interleukin 2, by locally expressed interleukin 1 β and NO, and by afferent vagal fibres. Moreover, synthesis of cortisol is modulated by locally expressed interleukin 6 and TNF α . Upregulated hormones help maintain cardiovascular homeostasis and cellular metabolism, and help wall-off foci of inflammation. Impaired endocrine responses to sepsis might result from cytokines, neuronal apoptosis, metabolic and ischaemic derangements in the hypothalamic-pituitary and adrenal glands, and drug administration.⁸³ Deficiencies in adrenal gland function⁸⁴ and vasopressin production⁶⁹ occur in about a half and a third of septic shock cases, respectively, contributing to hypotension and death.^{84–86} Other endocrine disorders during sepsis have unclear mechanisms and consequences (table 2).

Genetic polymorphisms

Various genetic polymorphisms are associated with increased susceptibility to infection and poor outcomes.

Target population	Main effects	Evidence
Prophylactic antibiotics		
Cancer patients with granulocytopenia	Prevents gram-negative and gram-positive bacteraemia	19 RCTs (n=2112)
Transurethral prostatic resection	Prevents bacteriuria and clinical septicæmia	32 RCTs (n=4260)
Cirrhotic patients with gastrointestinal bleeding	Prevents spontaneous bacterial peritonitis, bacteraemia, and death	5 RCTs (n=534)
Acute necrotising pancreatitis	Prevents severe sepsis and death	3 RCTs (n=160)
Enteral nutritional supplementation with nutrients such as L-arginine, n-3 essential fatty acids, L-glutamine, or branched-chain amino acids		
Elective major surgery—eg, for gastrointestinal cancer	Prevents superinfection	22 RCTs (n=2419)
Critically ill patients requiring enteral nutritional support—eg, trauma and burn patients	Prevents superinfection but might increase mortality	
Keep blood glucose concentrations between 4 and 6 mmol/L by intensive insulin therapy		
Surgical patients requiring prolonged stay in intensive care unit	Prevents bloodstream infections, sepsis-related organ dysfunctions, and death	1 RCT (n=1548)
Preventive strategies for iatrogenic infections		
All patients in intensive care unit	Prevents intravascular catheter-related sepsis, surgical site superinfection, nosocomial pneumonia	Several well designed RCTs, and epidemiological studies
Intravenous polyvalent immunoglobulins		
Patients undergoing surgery for colorectal cancer	Prevents postoperative sepsis	1 RCT (n=80)
Trauma patients	Prevents pneumonia and catheter-related sepsis	1 RCT (n=39)
Vaccines		
Children	Prevents serogroup C meningococcal disease	1 RCT (n=106)
Patients receiving chronic haemodialysis	Prevents <i>S aureus</i> bacteraemia	1 RCT (n=1804)
Children	Prevents <i>H influenzae</i> related death	4 RCTs (n=162,140)
Chronic bronchitis patients	Prevents seasonal acute exacerbations	6 RCTs (n=440)

RCT=randomised controlled trial.

Table 4: Preventive strategies for septic shock

Markers of susceptibility could include single nucleotide polymorphisms of genes encoding cytokines (eg, TNF, lymphotoxin- α , interleukin 10, interleukin 18, interleukin-1 receptor antagonist, interleukin 6, and interferon γ), cell surface receptors (eg, CD14, MD2, toll-like receptors 2 and 4, and Fc-gamma receptors II and III), lipopolysaccharide ligand (lipopolysaccharide binding protein), bactericidal permeability increasing protein), mannose-binding lectin, heat shock protein 70, angiotensin I-converting enzyme, plasminogen activator inhibitor, and caspase-12.⁹ This list is expected to grow, possibly providing new therapeutic targets or allowing an à la carte treatment approach. Use of genotype combinations could improve the identification of high-risk groups.⁸⁷

Mechanisms of organ dysfunction

The pathways leading to organ failures during sepsis can involve upregulation of inflammatory responses and neuroendocrine systems.^{70,88,89} Prompt recovery from organ failures in survivors and the normal anatomical appearance of the failed organs suggest that ischaemic and haemorrhagic damage are an uncommon mechanism. Alternatively, mediators such as TNF, interleukin 1 α , NO, and oxygen reactive species might inhibit the mitochondrial respiratory chain, inducing cellular dysoxia with reduced energy production, an effect aggravated by hormonal deficiencies.⁸⁹ Inflammatory mediators might also alter modulation by the autonomic nervous system of

biological oscillator functions,⁶⁹ leading to disruption of communication between organs, which can precede the development of shock⁹⁰ and multiorgan dysfunction.⁹¹ Lastly, excessive expression of tissue factor, decreased concentrations and activity of coagulation inhibitors (antithrombin III, activated protein C, and tissue factor pathway inhibitor), and insufficient fibrinolytic activity result in a procoagulant state that can interact with inflammatory mediators in a vicious circle, leading to organ failure.⁹²

Diagnosis

Diagnosis of septic shock in patients with systemic inflammatory response syndrome means that the infection must be recognised and proof obtained of a causal link between infection and organ failure and shock (table 3, figure 4).

There may be a clinically obvious infection, such as purpura fulminans, cellulitis, toxic shock syndrome, community-acquired pneumonia in a previously healthy individual, or a purulent discharge from a wound or normally sterile cavity (eg, bladder, peritoneal or pleural cavity, or cerebrospinal fluid). Otherwise, diagnosis of infection relies mainly on recovery of pathogens from blood or tissue cultures. However, cultures take 6–48 h and are negative in 30% of cases; furthermore, sepsis might be related to toxic agents produced by pathogens rather than to the pathogens themselves. Molecular tools such as PCR or microarray-based rapid (<4 h) detection of ten clinically significant

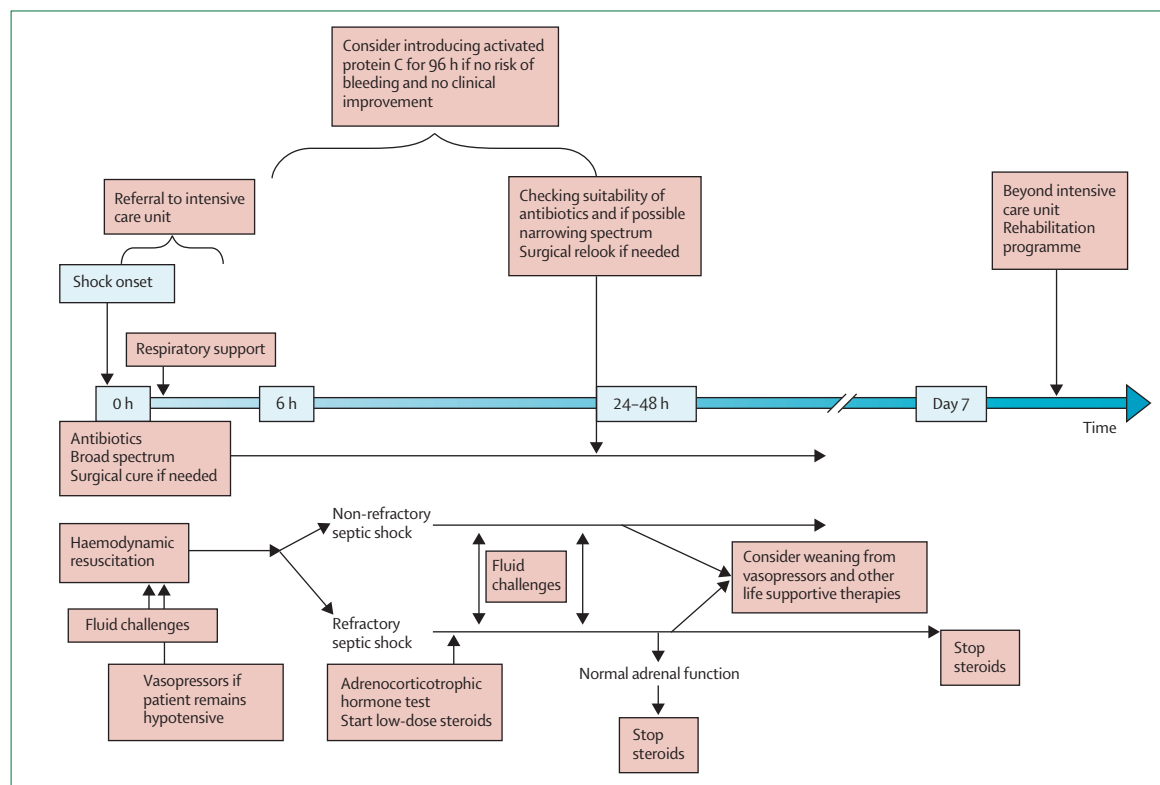


Figure 5: Principles of treatment in septic shock

Red boxes=interventions. Brackets=timing for interventions. Dotted lines=optional interventions.

bacterial species and of antimicrobial resistance will probably soon supersede conventional cultures.⁹³

The search for biomarkers of sepsis has been unsuccessful so far, and routine serum assays of endotoxin, procalcitonin, or other markers are not recommended. Indeed, although endotoxaemia is present in 30–40% of patients with gram-negative sepsis,⁹⁴ it can also be detected in gram-positive bacteraemia. Concentrations of procalcitonin in serum are usually increased in sepsis but fail to discriminate between infection and inflammation.⁹⁵ Nevertheless, the high negative predictive value of low serum procalcitonin ($<0.25 \mu\text{g/L}$) could allow discontinuation of unnecessary antibiotics.⁹⁶ The triggering receptor expressed on myeloid cells (TREM-1) is strongly and specifically expressed by neutrophils and macrophages from human tissues infected by bacteria or fungi.⁹⁷ Concentrations of soluble TREM-1 in bronchoalveolar lavage fluid of 5 ng/L or more can indicate ventilator-associated pneumonia,⁹⁸ and concentrations in plasma of 60 mg/L or more can indicate infection in patients with systemic inflammatory response syndrome.⁹⁹

Signs of tissue hypoperfusion include areas of mottled skin, oliguria, mental confusion, delayed capillary refill, and hyperlactacidaemia (table 3). However, detection of oliguria entails several hours of observation, and assessment of acute confusion

requires knowledge of previous cognitive function. Organ failure scores often ignore pre-existing organ function, mix physiological variables and interventions, use different definitions, and can be useless at the bedside.¹⁰⁰ For example, definitions of cardiovascular failure fail to discriminate between cardiac and circulatory dysfunction, although doing so is essential for titration of inotropic drugs and vasopressors. Brain dysfunction is defined according to the Glasgow coma score, which cannot be established in sedated patients. In practice, consensus definitions should be used when available—for acute lung injury and acute respiratory distress syndrome,¹⁰¹ or for disseminated intravascular coagulation.¹⁰² Other organ failures should be considered when introducing supportive therapy to maintain homeostasis (eg, renal replacement therapy). Recognition of brain dysfunction needs electrophysiological testing to produce data that are independent from the effects of sedation,¹⁰³ and cardiac dysfunction is best characterised by echocardiography.¹⁰⁴ Corticosteroid insufficiency should be diagnosed on the basis of a random total cortisol concentration in serum no greater than 415 nmol/L ($150 \mu\text{g/L}$) or a cortisol increment after corticotrophin no greater than 250 nmol/L ($90 \mu\text{g/L}$).^{84,105} When albumin concentrations are 25 g/L or less, the serum free-cortisol cutoff points for defining adrenal

	Target population	Main effects	Evidence
Controlling the source of infection			
Antibiotics	All patients	Appropriate antibiotics improve survival	Common sense, observational studies
Removal of infected and necrotic tissues	Patients with cellulitis, abscess, purulent wounds, infected devices	Improves survival	Common sense, observational studies
Management of shock			
Restoration of central venous pressure to 8–12 mm Hg, mean arterial pressure 65–90 mm Hg, and central venous oxygen saturation >70% with fluids, vasopressors, inotropic drugs, red blood cell transfusion, and mechanical ventilation Fluids: crystalloids versus albumin	All patients. Most effective if goal achieved within 6 h	Prevents organ dysfunction and death	1 RCT (n=263)
Crystalloids versus synthetic colloids		No difference in any outcome between serum saline and 5% albumin No evidence for differences in clinical outcomes	1 RCT (n=7000) 27 RCTs (n=2243) 1 continuing RCT (n=3000)
Vasopressors: Dopamine, norepinephrine or epinephrine Dopamine versus norepinephrine	Persistent hypotension after fluid administration	No evidence for difference in mortality	3 RCTs (n=62) 1 continuing RCT
Norepinephrine (dobutamine) versus epinephrine		No evidence for difference in mortality	2 RCTs (n= 52) 1 continuing RCT (n=330)
Management of organ dysfunction			
Daily versus alternate-day intermittent renal replacement treatment	Overt acute renal failure	Daily intermittent dialysis better than alternate-day dialysis for time to renal recovery and survival	1 RCT (n=160)
Intermittent versus continuous treatment Mechanical ventilation with low tidal volume 6–7 mL/kg ideal body weight	Acute lung injury or acute respiratory distress syndrome	No evidence for difference in mortality Ventilation with tidal volume 6–7 mL/kg better than ventilation with 10–15 mL/kg: more survivors and more ventilator free days	1 continuing RCT (n=400) 5 RCTs (n=1202)
Replacing or enhancing host responses			
Endocrine response Low-dose corticosteroids	Refractory septic shock and basal cortisol concentrations <150 µg/L or cortisol response to adrenocorticotrophin <90 µg/L	Improve haemodynamics; reduce shock duration, organ dysfunction, systemic inflammation, and mortality	5 RCTs (n=465) 1 continuing RCT (n=800)
Low-dose vasopressin	Patients not improving with or not meeting criteria for corticosteroids	Improve haemodynamics, reduce shock duration	4 RCTs (n=98) 1 continuing RCT (n=800)
Haemostasis response Drotrecogin alfa	Undisputable septic shock not improving with or not meeting criteria for corticosteroids, and with APACHE II >24, and at least one new (<48 h) organ dysfunction (eg, acute lung injury or acute respiratory distress syndrome or acute renal failure and no risk of bleeding)	Improve haemodynamics, reduce shock duration, organ dysfunction, and mortality	1 RCT (n=1690)

RCT=randomised controlled trial.

Table 5: Treatments for septic shock

insufficiency are 55 nmol/L (20 µg/L) at baseline and 85 nmol/L (31 µg/L) after corticotrophin.¹⁰⁶ However, in everyday practice, unbound plasma cortisol must be derived from the total cortisol and corticosteroid-binding globulin concentrations.¹⁰⁷ No evidence lends support to routine screening for other endocrine dysfunctions.

Although need for vasopressors to maintain arterial pressure is widely used as the criterion for shock,¹ low central venous oxygen saturation (<70%),¹⁰⁸ direct non-invasive visualisation of altered microcirculation,^{109,110} or impaired cardiovascular variability⁹⁰ could provide earlier diagnosis.

Establishing a causal link between infection and organ dysfunction is difficult. The likelihood of infection and the presence of another acute illness such

as trauma, burns, pancreatitis, cardiac disease, or poisoning should be taken into account (figure 4). A definite diagnosis of septic shock can be made when there is a clinically apparent and microbiologically documented infection and no other acute illness. Septic shock is likely when clinically apparent infection is present without microbial documentation and without any other acute illness. Septic shock is unlikely when the diagnosis of infection is in doubt, no microbiological documentation is present, and another illness could explain the organ dysfunction. High concentrations of procalcitonin or TREM-1 in tissue can assist in the diagnosis of culture-negative septic shock, and concentrations of procalcitonin in serum lower than 0.25 µg/L can further rule out infection when septic shock is unlikely.

Treatment

Interventions that can prevent septic shock in some populations include prophylactic antibiotics,^{111,112} maintenance of blood glucose concentrations between 4 and 6 mmol/L,¹¹³ selective digestive-tract decontamination,¹¹⁴ strategies for prevention of iatrogenic infections,¹¹⁵ and immune therapies such as vaccines^{116,117} and intravenous immunoglobulin (table 4).^{118,119} Enteral nutritional supplementation, especially with L-arginine, can reduce infection rate after elective surgery and in critically ill patients, but can also increase mortality in such patients.¹²⁰ The search for vaccines to lipopolysaccharide failed to overcome several hurdles, including identification of target populations and target epitopes for antibodies, as well as rapid generation of antibodies in protective amounts.

Patients must be referred promptly to an intensive care unit where management includes careful nursing, immediate control of infection and haemodynamic status, and support to failing organs and to immune, neuroendocrine, and haemostasis responses. After discharge, appropriate rehabilitation and long-term follow-up are mandatory (figure 5).

Rapid removal of infected tissues or devices combined with antibiotic treatment is the key to ensuring survival, even though the evidence supporting this approach is merely common sense: indeed, Ambroise Paré saved lives by amputating soldiers' gangrenous limbs on the battlefield and Fleming did so by discovering penicillin (table 5). Prospective cohort studies showed an increase in mortality of 1·4–8 times with inadequate initial antibiotic therapy.^{121,122}

To manage shock and organ dysfunction, fluid resuscitation should be initiated promptly and guided by monitoring of the central venous oxygen saturation, a surrogate of global tissue dysoxia, in addition to clinical signs (table 5).^{108,123} Fluid challenges can be repeated until cardiac output increases by more than 10% and as long as central venous pressure increases less than 3 mm Hg. Other monitoring tools include right-heart catheterisation, transpulmonary thermodilution techniques, echocardiography, and pulse pressure or vena cava variability,¹²³ and physicians should use the method with which they are familiar. A trial of fluid replacement in 7000 critically ill patients showed no difference in mortality between crystalloids and albumin,¹²⁴ and an ongoing trial (CRISTAL) is comparing synthetic colloids with crystalloids. For now, crystalloids and synthetic colloids can be used alone or in combination.

Of the vasopressors, dopamine or norepinephrine is recommended as the first-line drug, although phase II trials have yielded conflicting results.^{123,125} Two large continuing trials in patients with septic shock are comparing epinephrine to combined dobutamine and norepinephrine (CATS) or dopamine to norepinephrine (DeBacker D, personal communication). At present, physicians should use their preferred drug (table 5).

	Molecules	Development phase
Lipopolysaccharide	Cationic antimicrobial protein 18	Experimental
	Synthetic analogues of lipid A, E5564	Clinical, phase II
	Recombinant human lipoproteins	Experimental
	Monoclonal antibodies to CD14	Clinical, phase I
Late proinflammatory mediators	Antibody to high mobility group box 1, DNA-binding A box, ethyl pyruvate	Experimental
	Anti-macrophage migration inhibitory factor	Experimental
	Blockade of either C5a or C5a receptor	Experimental
Complement system cascade		Experimental
Apoptosis	Anti-caspase	Experimental
	Blockade of Fas/Fas ligand	
	with Fas receptor fusion protein	Experimental
	Metoclopramide	Experimental
	Over-expression of B-cell lymphoma/leukaemia-2	Experimental
Poly-ADP-ribose synthase	Inhibitors of this target	Experimental
Inducible NO synthase	2-aminopyridines, ONO-1714, polyphenolic flavonoid antioxidant, aminoguanidine, L-N6-(1-iminoethyl)-lysine	Experimental
Autonomic nervous system	Vagal nerve stimulation	Experimental
Others	High mobility group-CoA reductase inhibitors	Experimental
	Blockade of endothelin-receptor	Experimental
	Calpain inhibitors	Experimental
	A _{2A} adenosine receptor agonists	Experimental

Table 6: Putative future targets and treatments

When hypotension results mainly from myocardial depression, inotropic agents can be used first. Vasopressors should be titrated to quickly restore systemic mean arterial pressure to 60–90 mm Hg, depending on whether the patient had pre-existing hypertension. Secondary endpoints that need monitoring include cardiac performance, tissue dysoxia (eg, lactate), and microcirculation as assessed by capillary refilling time or by sublingual capnography. Optimisation of haemodynamic status could require blood transfusion and, occasionally, vasodilators.^{108,109} Patients should be treated with oxygen, and when they have acute lung injury or acute respiratory distress syndrome, with invasive mechanical ventilation with a tidal volume of 6–7 mL/kg of ideal body weight.¹²⁶ Daily haemodialysis¹²⁷ or continuous venovenous haemofiltration with an ultrafiltration rate of 35–45 mL/kg per h¹²⁸ should be used in patients with overt acute renal failure (table 5).⁸⁸

The first attempts to combat inflammation in patients with septic shock relied on non-selective drugs—ie, high-dose corticosteroids¹²⁹ and non-steroidal anti-inflammatory drugs.¹³⁰ These drugs failed to improve survival. Monoclonal antibodies (HA-1A, E5) targeting lipopolysaccharide^{131,132} were tested but proved ineffective because of their weak biological activity.¹³³ By contrast, recombinant bactericidal permeability-increasing protein significantly improved functional outcome in children with severe meningococcal septicaemia (77% of 190 children recovered their preillness level of function compared with 66% of 203 placebo-treated controls, $p=0\cdot019$).¹³⁴ Other lipopolysaccharide-targeting drugs are being investigated, such as cationic antimicrobial protein 18 (which is also bactericidal),¹³⁵ synthetic analogues of lipid A, E5564,¹³⁶ human lipoproteins which also exert anti-inflammatory effects independently from binding to

lipopolysaccharide,¹³⁷ and recombinant monoclonal antibody to CD14.¹³⁸

Second-generation drugs for septic shock blindly and massively block one factor in the inflammatory cascade, for instance, TNF α , interleukin 1, platelet activating factor, adhesion molecules, arachidonic acid metabolites, oxygen free radicals, bradykinin, phosphodiesterase and C1 esterase, or NO synthase. They failed to improve survival.¹³⁹ However, because they are biologically active, they might prove beneficial when used in specific strategies. A meta-analysis of 10 sepsis trials (6821 patients) showed an absolute reduction in mortality of 3.5% with antiTNF drugs.¹³⁹ Carriers of the TNFB2 allele are at risk for lethal septic shock,⁹ indicating that antibodies to TNF should be reassessed in this population. Upregulation of inducible NO synthase contributes to hypotension and organ dysfunction during sepsis.¹²³ However, constitutive NO synthase is essential for homeostasis, and activity of inducible NO synthase is mainly confined to infected tissues.⁶⁸ Thus, although non-selective inhibition of NO synthase was associated with increased mortality from septic shock,¹⁴⁰ selective inhibition of inducible NO synthase deserves to be investigated. Future therapeutic targets could also include late mediators such as HMGB1 or macrophage migration inhibitory factor, complement C5a and its receptor, or apoptosis (table 6).

Polyvalent intravenous immunoglobulins modulate the expression and function of Fc receptors, activation of complement and cytokine networks, production of idiotype antibodies, and activation, differentiation, and effector functions of T and B cells.¹⁴¹ A meta-analysis showed reduced mortality with polyclonal immunoglobulins (n=492; relative risk [RR] 0.64; 95% CI 0.51–0.80). However, a sensitivity analysis on high-quality trials found no evidence that immunoglobulins were beneficial,¹⁴² highlighting the need for adequately powered trials of immunoglobulins in septic shock. Similarly, the clinical benefit from treatment with interferon γ and granulocyte macrophage colony stimulating factor remains uncertain,¹³⁹ although these drugs might correct a number of immune function variables.^{143,144}

Recent approaches rely on replacement of hormones or coagulation inhibitors. A meta-analysis¹²⁹ showed that hydrocortisone in doses from 200–300 mg for 5 days or more reduced duration of shock, systemic inflammation, and mortality (RR 0.80; 95% CI 0.67–0.95) without causing harm (table 5). Only patients with refractory septic shock and adrenal insufficiency benefit from hydrocortisone, and 50 μ g/day oral fludrocortisone can be added.¹⁴⁵ A continuing trial (CORTICUS) is investigating the risk to benefit ratio of hydrocortisone in non-refractory septic shock. Vasopressin replacement therapy in doses ranging from 0.01–0.04 IU/min improved haemodynamics and decreased catecholamine requirements (table 5).^{146–149} However, vasopressin might induce myocardial, cutaneous, or mesenteric vasocon-

striction and should not be used until the results of the VAST trial are reported.

Recombinant human activated protein C (drotrecogin alfa, 24 μ g/kg per h for 96 h) provided a 6% reduction in 28-day mortality from sepsis with at least one recent (<48 h) organ dysfunction.¹⁵⁰ A trial of this drug in 11 000 patients with sepsis inducing one organ dysfunction (ADDRESS) was stopped prematurely because of inefficacy. Drotrecogin alfa should be given for septic shock requiring respiratory or renal support, provided there is no risk of bleeding, as detailed in the PROWESS trial (table 5).¹⁵⁰ Neither anti-thrombin III¹⁵¹ nor tissue factor pathway inhibitor⁵⁴ have proved beneficial in patients with sepsis. Significant interactions were noted between heparin and activated protein C, anti-thrombin III, and tissue factor pathway inhibitor, masking treatment benefits and promoting bleeding. Continuing trials are reassessing these drugs in heparin-free patients. Meanwhile, anti-thrombin III and tissue factor pathway inhibitor should not be used, and heparin should be avoided during infusion of drotrecogin alfa. Whether heparin is beneficial in patients with sepsis remains unclear.

Outcomes

Mortality

Short-term mortality from septic shock has decreased significantly in recent years. In one study, mortality fell from 62% in the early 1990s to 56% in 2000.⁵ Mortality varies from 35% to 70%, depending on factors such as age, sex, ethnic origin, comorbidities, presence of acute lung injury or acute respiratory distress syndrome or renal failure, whether the infection is nosocomial or polymicrobial, and whether a fungus is the causative agent.^{3–6} Comparisons with matched patients without sepsis have shown that the mortality attributable to septic shock is 26%.⁵

Data for long-term mortality in patients with septic shock are scarce. In one retrospective study, the mean lifespan of short-term survivors was reduced from 8 to 4 years.¹⁵² A trial including a prospective estimation of one-year survival¹⁴⁵ suggested that about 20% of hospital survivors could die within the first year.

Morbidity

In the short-term, septic shock increases the length of stay in the intensive care unit and hospital compared with patients without sepsis,^{5,6} and results in more organ dysfunction and greater use of the unit's resources, including right-heart catheterisation, mechanical ventilation, renal replacement therapy, vasopressors, and nurse workload.⁵ Septic shock also increases the risk of super-infections⁶ and neuromuscular complications associated with intensive care.¹⁵³ Long-term sequels have received less research attention. They might include physical disability related to muscle weakness and post-traumatic stress disorders.

Their exact frequency and mechanisms have not been established.

The future

Septic shock remains a major source of short-term and long-term morbidity and mortality, and places a large burden on the healthcare system. The recent identification in people of molecules that sense microbial determinants has been an important step in understanding the molecular and cellular basis of sepsis. Characterisation of the links between inflammation, coagulation, and the immune and neuroendocrine systems have led to international guidelines recommending the use of drotrecogin alfa and low-dose hydrocortisone in the early management of septic shock. New knowledge about apoptosis, leucocyte reprogramming, epithelial dysfunction, and factors involved in sepsis holds promise for the development of new therapeutic approaches. Although improvement of immediate survival is a key goal, physicians are also becoming aware that specific rehabilitation programmes and long-term follow-up are essential.

Conflict of interest statement

We declare that we have no conflict of interest.

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We dedicate this review to the late Lerner B Hinshaw, who participated in the D-Day landings in Normandy, and who made a major contribution to understanding of septic shock.

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