REVIEW ARTICLE

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Severe Sepsis and Septic Shock

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SEPSIS IS ONE OF THE OLDEST AND MOST ELUSIVE SYNDROMES IN MEDICINE. Hippocrates claimed that sepsis (σήψις) was the process by which flesh rots, swamps generate foul airs, and wounds fester.[1] Galen later considered sepsis a laudable event, necessary for wound healing.[2] With the confirmation of germ theory by Semmelweis, Pasteur, and others, sepsis was recast as a systemic infection, often described as "blood poisoning," and assumed to be the result of the host's invasion by pathogenic organisms that then spread in the bloodstream. However, with the advent of modern antibiotics, germ theory did not fully explain the pathogenesis of sepsis: many patients with sepsis died despite successful eradication of the inciting pathogen. Thus, researchers suggested that it was the host, not the germ, that drove the pathogenesis of sepsis.[3]

In 1992, an international consensus panel defined sepsis as a systemic inflammatory response to infection, noting that sepsis could arise in response to multiple infectious causes and that septicemia was neither a necessary condition nor a helpful term.[4] Instead, the panel proposed the term "severe sepsis" to describe instances in which sepsis is complicated by acute organ dysfunction, and they codified "septic shock" as sepsis complicated by either hypotension that is refractory to fluid resuscitation or by hyperlactatemia. In 2003, a second consensus panel endorsed most of these concepts, with the caveat that signs of a systemic inflammatory response, such as tachycardia or an elevated white-cell count, occur in many infectious and noninfectious conditions and therefore are not helpful in distinguishing sepsis from other conditions.[5] Thus, "severe sepsis" and "sepsis" are sometimes used interchangeably to describe the syndrome of infection complicated by acute organ dysfunction.

INCIDENCE AND CAUSES

The incidence of severe sepsis depends on how acute organ dysfunction is defined and on whether that dysfunction is attributed to an underlying infection. Organ dysfunction is often defined by the provision of supportive therapy (e.g., mechanical ventilation), and epidemiologic studies thus count the "treated incidence" rather than the actual incidence. In the United States, severe sepsis is recorded in 2% of patients admitted to the hospital. Of these patients, half are treated in the intensive care unit (ICU), representing 10% of all ICU admissions.[6,7] The number of cases in the United States exceeds 750,000 per year[7] and was recently reported to be rising.[8] However, several factors — new *International Classification of Diseases, 9th Revision* (ICD-9) coding rules, confusion over the distinction between septicemia and severe sepsis, the increasing capacity to provide intensive care, and increased awareness and surveillance — confound the interpretation of temporal trends.

Studies from other high-income countries show similar rates of sepsis in the ICU.[9] The incidence of severe sepsis outside modern ICUs, especially in parts of

the world in which ICU care is scarce, is largely unknown. Extrapolating from treated incidence rates in the United States, Adhikari et al. estimated up to 19 million cases worldwide per year.[10] The true incidence is presumably far higher.

Severe sepsis occurs as a result of both community-acquired and health care–associated infections. Pneumonia is the most common cause, accounting for about half of all cases, followed by intraabdominal and urinary tract infections.[7,8,11,12] Blood cultures are typically positive in only one third of cases, and in up to a third of cases, cultures from all sites are negative.[7,11,13,14] *Staphylococcus aureus* and *Streptococcus pneumoniae* are the most common gram-positive isolates, whereas *Escherichia coli*, klebsiella species, and *Pseudomonas aeruginosa* predominate among gram-negative isolates.[11,14] An epidemiologic study of sepsis showed that during the period from 1979 to 2000, gram-positive infections overtook gram-negative infections.[15] However, in a more recent study involving 14,000 ICU patients in 75 countries, gram-negative bacteria were isolated in 62% of patients with severe sepsis who had positive cultures, gram-positive bacteria in 47%, and fungi in 19%.[12]

Risk factors for severe sepsis are related both to a patient's predisposition for infection and to the likelihood of acute organ dysfunction if infection develops. There are many well-known risk factors for the infections that most commonly precipitate severe sepsis and septic shock, including chronic diseases (e.g., the acquired immunodeficiency syndrome, chronic obstructive pulmonary disease, and many cancers) and the use of immunosuppressive agents.[7] Among patients with such infections, however, the risk factors for organ dysfunction are less well studied but probably include the causative organism and the patient's genetic composition, underlying health status, and preexisting organ function, along with the timeliness of therapeutic intervention.[16] Age, sex, and race or ethnic group all influence the incidence of severe sepsis, which is higher in infants and elderly persons than in other age groups, higher in males than in females, and higher in blacks than in whites.[7,17]

There is considerable interest in the contribution of host genetic characteristics to the incidence and outcome of sepsis, in part because of strong evidence of inherited risk factors.[18] Many studies have focused on polymorphisms in genes encoding proteins implicated in the pathogenesis of sepsis, including cytokines and other mediators involved in innate immunity, coagulation, and fibrinolysis. However, findings are often inconsistent, owing at least in part to the heterogeneity of the patient populations studied.[19,20] Although a recent genomewide association study[21] explored drug responsiveness in sepsis, no such large-scale studies of susceptibility to or outcome of sepsis have been performed.

CLINICAL FEATURES

The clinical manifestations of sepsis are highly variable, depending on the initial site of infection, the causative organism, the pattern of acute organ dysfunction, the underlying health status of the patient, and the interval before initiation of treatment. The signs of both infection and organ dysfunction may be subtle, and thus the most recent international consensus guidelines provide a long list of warning signs of incipient sepsis (Table 1).[5] Acute organ dysfunction most commonly affects the respiratory and cardiovascular systems. Respiratory compromise is classically manifested as the acute respiratory distress syndrome (ARDS), which is defined as hypoxemia with bilateral infiltrates of noncardiac origin.[22] Cardiovascular compromise is manifested primarily as hypotension or an elevated serum lactate level. After adequate volume expansion, hypotension frequently persists, requiring the use of vasopressors, and myocardial dysfunction may occur.[23]

The brain and kidneys are also often affected. Central nervous system dysfunction is typically manifested as obtundation or delirium. Imaging studies generally show no focal lesions, and findings on electroencephalography are usually consistent with nonfocal encephalopathy. Critical illness polyneuropathy and myopathy are also common, especially in patients with a prolonged ICU stay.[24] Acute kidney injury is manifested as decreasing urine output and an increasing serum creatinine level and frequently requires treatment with renal-replacement therapy. Paralytic ileus, elevated aminotransferase levels, altered glycemic control, thrombocytopenia and disseminated intravascular coagulation, adrenal dysfunction, and the euthyroid sick syndrome are all common in patients with severe sepsis.[5]

Table 1. Diagnostic Criteria for Sepsis, Severe Sepsis, and Septic Shock.*

Sepsis (documented or suspected infection plus ≥1 of the following)†
General variables
Fever (core temperature, >38.3°C)
Hypothermia (core temperature, <36°C)
Elevated heart rate (>90 beats per min or >2 SD above the upper limit of the normal range for age)
Tachypnea
Altered mental status
Substantial edema or positive fluid balance (>20 ml/kg of body weight over a 24-hr period)
Hyperglycemia (plasma glucose, >120 mg/dl [6.7 mmol/liter]) in the absence of diabetes
Inflammatory variables
Leukocytosis (white-cell count, >12,000/mm^3)
Leukopenia (white-cell count, <4000/mm^3)
Normal white-cell count with >10% immature forms
Elevated plasma C-reactive protein (>2 SD above the upper limit of the normal range)
Elevated plasma procalcitonin (>2 SD above the upper limit of the normal range)
Hemodynamic variables
Arterial hypotension (systolic pressure, <90 mm Hg; mean arterial pressure, <70 mm Hg; or decrease in systolic pressure of >40 mm Hg in adults or to >2 SD below the lower limit of the normal range for age)
Elevated mixed venous oxygen saturation (>70%)‡
Elevated cardiac index (>3.5 liters/min/square meter of body-surface area)§
Organ-dysfunction variables
Arterial hypoxemia (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, <300)
Acute oliguria (urine output, <0.5 ml/kg/hr or 45 ml/hr for at least 2 hr)
Increase in creatinine level of >0.5 mg/dl (>44 μmol/liter)
Coagulation abnormalities (international normalized ratio, >1.5; or activated partial-thromboplastin time, >60 sec)
Paralytic ileus (absence of bowel sounds)
Thrombocytopenia (platelet count, <100,000/mm^3)
Hyperbilirubinemia (plasma total bilirubin, >4 mg/dl [68 μmol/liter])
Tissue-perfusion variables
Hyperlactatemia (lactate, >1 mmol/liter)
Decreased capillary refill or mottling
Severe sepsis (sepsis plus organ dysfunction)
Septic shock (sepsis plus either hypotension [refractory to intravenous fluids] or hyperlactatemia)¶

* Data are adapted from Levy et al.[5]
† In children, diagnostic criteria for sepsis are signs and symptoms of inflammation plus infection with hyperthermia or hypothermia (rectal temperature, >38.5°C or <35°C, respectively), tachycardia (may be absent with hypothermia), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.
‡ A mixed venous oxygen saturation level of more than 70% is normal in newborns and children (pediatric range, 75 to 80%).
§ A cardiac index ranging from 3.5 to 5.5 liters per minute per square meter is normal in children.
¶ Refractory hypotension is defined as either persistent hypotension or a requirement for vasopressors after the administration of an intravenous fluid bolus.

OUTCOME

Before the introduction of modern intensive care with the ability to provide vital-organ support, severe sepsis and septic shock were typically lethal. Even with intensive care, rates of in-hospital death from septic shock were often in excess of 80% as recently as 30 years ago.[25] However, with advances in training, better surveillance and monitoring, and prompt initiation of therapy to treat the underlying infection and support failing organs, mortality is now closer to 20 to 30% in

many series.[7,26] With decreasing death rates, attention has focused on the trajectory of recovery among survivors. Numerous studies have suggested that patients who survive to hospital discharge after sepsis remain at increased risk for death in the following months and years. Those who survive often have impaired physical or neurocognitive functioning, mood disorders, and a low quality of life.[27] In most studies, determining the causal role of sepsis in such subsequent disorders has been difficult. However, a recent analysis of the Health and Retirement Study, involving a large, longitudinal cohort of aging Americans, suggested that severe sepsis significantly accelerated physical and neurocognitive decline.[28]

PATHOPHYSIOLOGY

HOST RESPONSE

As the concept of the host theory emerged, it was first assumed that the clinical features of sepsis were the result of overly exuberant inflammation. Later, Bone et al.[29] advanced the idea that the initial inflammatory response gave way to a subsequent "compensatory antiinflammatory response syndrome." However, it has become apparent that infection triggers a much more complex, variable, and prolonged host response, in which both proinflammatory and antiinflammatory mechanisms can contribute to clearance of infection and tissue recovery on the one hand and organ injury and secondary infections on the other.[30] The specific response in any patient depends on the causative pathogen (load and virulence) and the host (genetic characteristics and coexisting illnesses), with differential responses at local, regional, and systemic levels (Fig. 1). The composition and direction of the host response probably change over time in parallel with the clinical course. In general, proinflammatory reactions (directed at eliminating invading pathogens) are thought to be responsible for collateral tissue damage in severe sepsis, whereas antiinflammatory responses (important for limiting local and systemic tissue injury) are implicated in the enhanced susceptibility to secondary infections.

INNATE IMMUNITY

Knowledge of pathogen recognition has increased tremendously in the past decade. Pathogens activate immune cells through an interaction with pattern-recognition receptors, of which four main classes — toll-like receptors, C-type lectin receptors, retinoic acid inducible gene 1–like receptors, and nucleotide-binding oligomerization domain–like receptors — have been identified, with the last group partially acting in protein complexes called inflammasomes (Fig. 1).[31] These receptors recognize structures that are conserved among microbial species, so-called pathogen-associated molecular patterns, resulting in the up-regulation of inflammatory gene transcription and initiation of innate immunity. The same receptors also sense endogenous molecules released from injured cells, so-called damage-associated molecular patterns, or alarmins, such as high-mobility group protein B1, S100 proteins, and extracellular RNA, DNA, and histones.[32] Alarmins are also released during sterile injury such as trauma, giving rise to the concept that the pathogenesis of multiple organ failure in sepsis is not fundamentally different from that in noninfectious critical illness.[32]

COAGULATION ABNORMALITIES

Severe sepsis is almost invariably associated with altered coagulation, frequently leading to disseminated intravascular coagulation.[33] Excess fibrin deposition is driven by coagulation through the action of tissue factor, a transmembrane glycoprotein expressed by various cell types; by impaired anticoagulant mechanisms, including the protein C system and antithrombin; and by compromised fibrin removal owing to depression of the fibrinolytic system (Fig. 2).[33] Protease-activated receptors (PARs) form the molecular link between coagulation and inflammation. Among the four subtypes that have been identified, PAR1 in particular is implicated in sepsis.[33] PAR1 exerts cytoprotective effects when stimulated by activated protein C or low-dose thrombin but exerts disruptive effects on endothelial-cell barrier function when activated by high-dose thrombin.[34] The protective effect of activated protein C in animal models of sepsis is dependent on its capacity to activate PAR1 and not on its anticoagulant properties.[34]

ANTIINFLAMMATORY MECHANISMS AND IMMUNOSUPPRESSION

The immune system harbors humoral, cellular, and neural mechanisms that attenuate the potentially harmful effects of the proinflammatory response (Fig. 1).[30] Phagocytes can switch to an

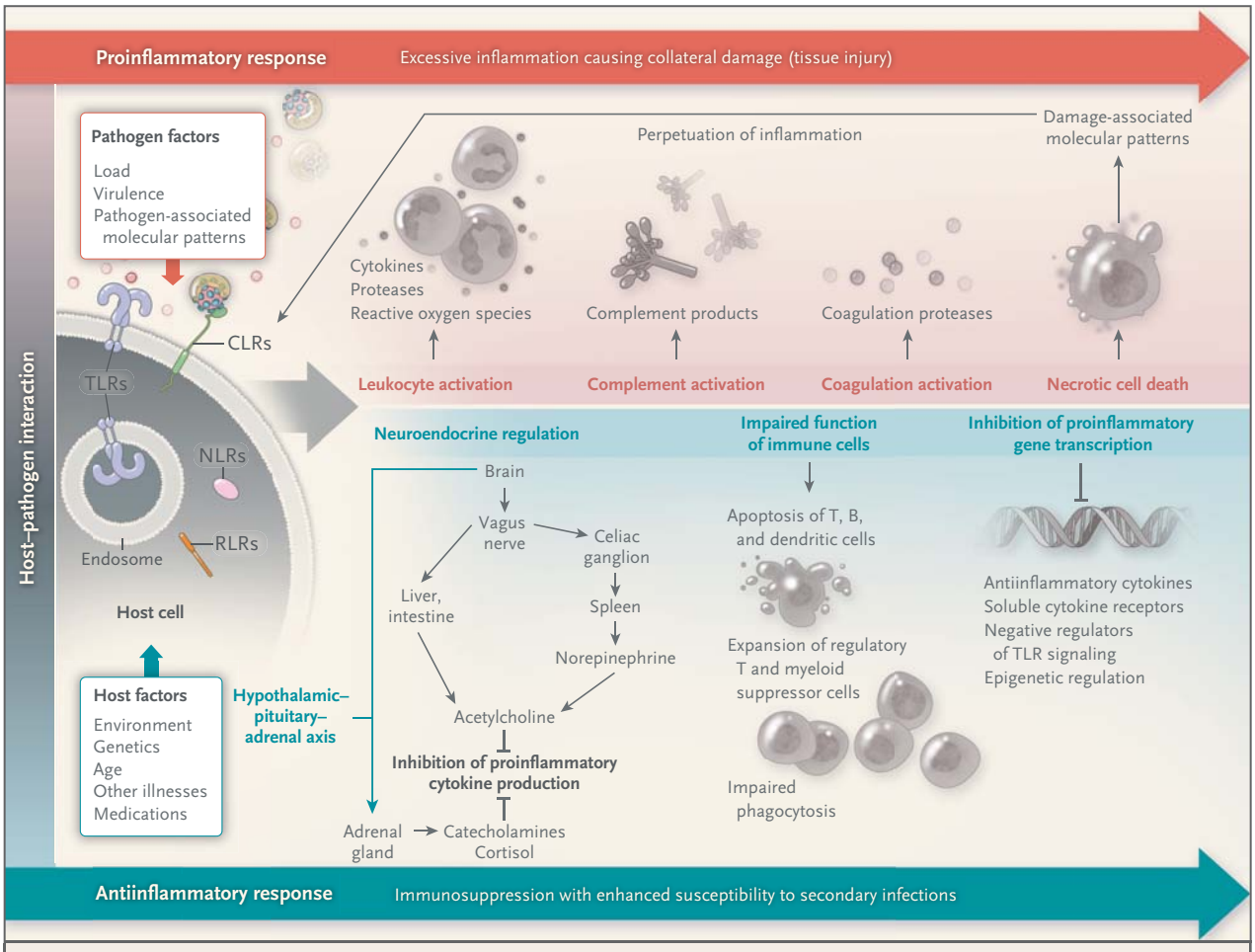

Figure 1. The Host Response in Severe Sepsis.

The host response to sepsis is characterized by both proinflammatory responses (top of panel, in red) and antiinflammatory immunosuppressive responses (bottom of panel, in blue). The direction, extent, and duration of these reactions are determined by both host factors (e.g., genetic characteristics, age, coexisting illnesses, and medications) and pathogen factors (e.g., microbial load and virulence). Inflammatory responses are initiated by interaction between pathogen-associated molecular patterns expressed by pathogens and pattern-recognition receptors expressed by host cells at the cell surface (toll-like receptors [TLRs] and C-type lectin receptors [CLRs]), in the endosome (TLRs), or in the cytoplasm (retinoic acid inducible gene 1–like receptors [RLRs] and nucleotide-binding oligomerization domain–like receptors [NLRs]). The consequence of exaggerated inflammation is collateral tissue damage and necrotic cell death, which results in the release of damage-associated molecular patterns, so-called danger molecules that perpetuate inflammation at least in part by acting on the same pattern-recognition receptors that are triggered by pathogens.

antiinflammatory phenotype that promotes tissue repair, and regulatory T cells and myeloid-derived suppressor cells further reduce inflammation. In addition, neural mechanisms can inhibit inflammation.[35] In the so-called neuroinflammatory reflex, sensory input is relayed through the afferent vagus nerve to the brain stem, from which the efferent vagus nerve activates the splenic nerve in the celiac plexus, resulting in norepinephrine release in the spleen and acetylcholine secretion by a subset of CD4+ T cells. The acetylcholine release targets $\alpha 7$ cholinergic receptors on macrophages, suppressing the release of proinflammatory cytokines.[36] In animal models of sepsis,[35] disruption of this neural-based system by vagotomy increases susceptibility to endotoxin shock, whereas stimulation of the efferent vagus nerve or $\alpha 7$ cholinergic receptors attenuates systemic inflammation.

Patients who survive early sepsis but remain dependent on intensive care have evidence of immunosuppression, in part reflected by reduced

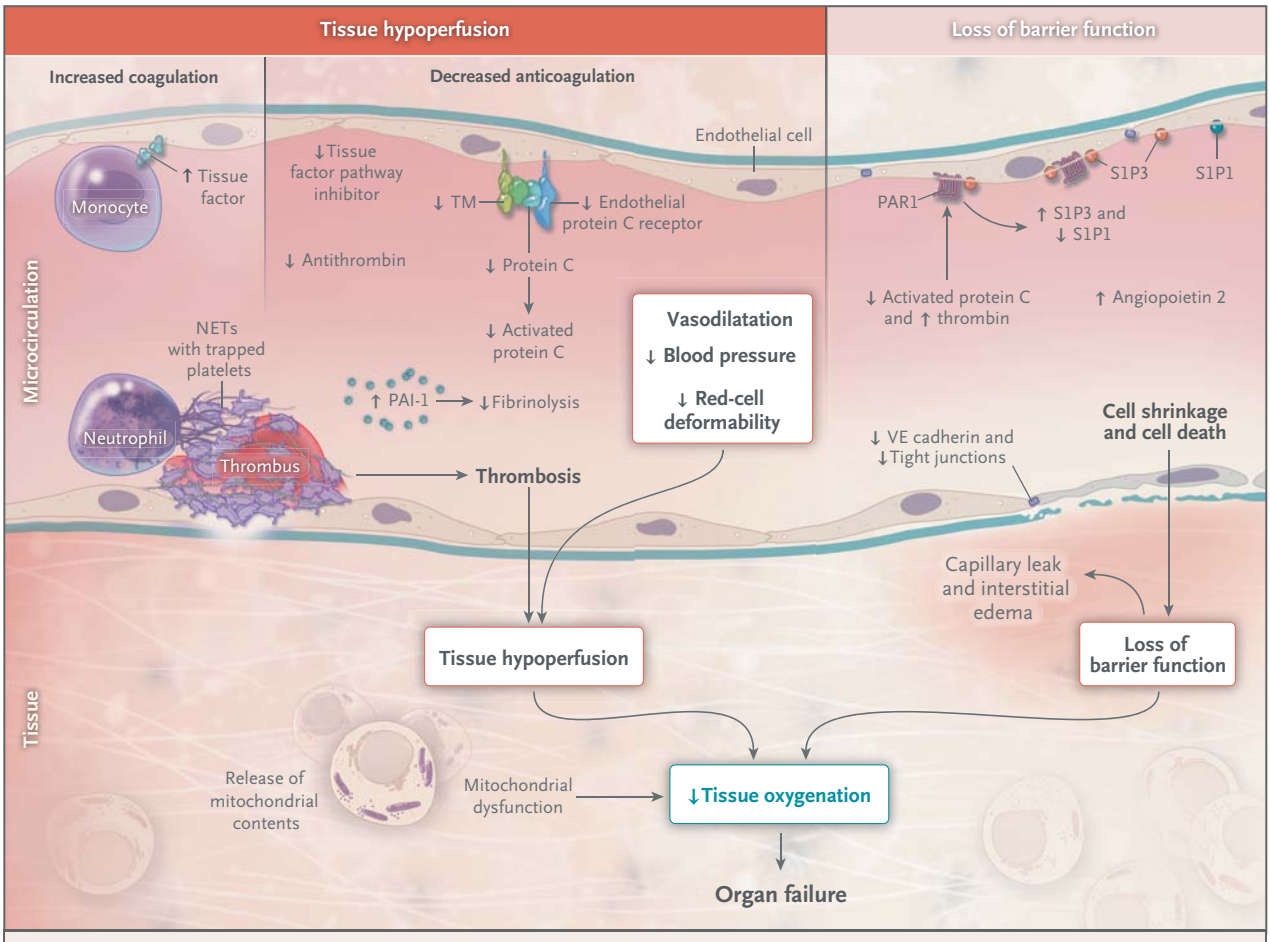

Figure 2. Organ Failure in Severe Sepsis and Dysfunction of the Vascular Endothelium and Mitochondria.

Sepsis is associated with microvascular thrombosis caused by concurrent activation of coagulation (mediated by tissue factor) and impairment of anticoagulant mechanisms as a consequence of reduced activity of endogenous anticoagulant pathways (mediated by activated protein C, antithrombin, and tissue factor pathway inhibitor), plus impaired fibrinolysis owing to enhanced release of plasminogen activator inhibitor type 1 (PAI-1). The capacity to generate activated protein C is impaired at least in part by reduced expression of two endothelial receptors: thrombomodulin (TM) and the endothelial protein C receptor. Thrombus formation is further facilitated by neutrophil extracellular traps (NETs) released from dying neutrophils. Thrombus formation results in tissue hypoperfusion, which is aggravated by vasodilatation, hypotension, and reduced red-cell deformability. Tissue oxygenation is further impaired by the loss of barrier function of the endothelium owing to a loss of function of vascular endothelial (VE) cadherin, alterations in endothelial cell-to-cell tight junctions, high levels of angiopoietin 2, and a disturbed balance between sphingosine-1 phosphate receptor 1 (S1P1) and S1P3 within the vascular wall, which is at least in part due to preferential induction of S1P3 through protease activated receptor 1 (PAR1) as a result of a reduced ratio of activated protein C to thrombin. Oxygen use is impaired at the subcellular level because of damage to mitochondria from oxidative stress.

expression of HLA-DR on myeloid cells.[37] These patients frequently have ongoing infectious foci, despite antimicrobial therapy, or reactivation of latent viral infection.[38,39] Multiple studies have documented reduced responsiveness of blood leukocytes to pathogens in patients with sepsis,[30] findings that were recently corroborated by postmortem studies revealing strong functional impairments of splenocytes obtained from patients who had died of sepsis in the ICU.[37] Besides the spleen, the lungs also showed evidence of immunosuppression; both organs had enhanced expression of ligands for T-cell inhibitory receptors on parenchymal cells.[37] Enhanced apoptosis, especially of B cells, CD4+ T cells, and follicular dendritic cells, has been implicated in sepsis-associated immunosuppression and death.[40,41] Epigenetic regulation of gene expres-

Table 2. Guidelines for the Treatment of Severe Sepsis and Septic Shock from the Surviving Sepsis Campaign.*

Element of Care	Grade†
Resuscitation	
Begin goal-directed resuscitation during first 6 hr after recognition	1C
Begin initial fluid resuscitation with crystalloid and consider the addition of albumin	1B
Consider the addition of albumin when substantial amounts of crystalloid are required to maintain adequate arterial pressure	2C
Avoid hetastarch formulations	1C
Begin initial fluid challenge in patients with tissue hypoperfusion and suspected hypovolemia, to achieve ≥30 ml of crystalloids per kilogram of body weight‡	1C
Continue fluid-challenge technique as long as there is hemodynamic improvement	1C
Use norepinephrine as the first-choice vasopressor to maintain a mean arterial pressure of ≥65 mm Hg	1B
Use epinephrine when an additional agent is needed to maintain adequate blood pressure	2B
Add vasopressin (at a dose of 0.03 units/min) with weaning of norepinephrine, if tolerated	UG
Avoid the use of dopamine except in carefully selected patients (e.g., patients with a low risk of arrhythmias and either known marked left ventricular systolic dysfunction or low heart rate)	2C
Infuse dobutamine or add it to vasopressor therapy in the presence of myocardial dysfunction (e.g., elevated cardiac filling pressures or low cardiac output) or ongoing hypoperfusion despite adequate intravascular volume and mean arterial pressure	1C
Avoid the use of intravenous hydrocortisone if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability; if hydrocortisone is used, administer at a dose of 200 mg/day	2C
Target a hemoglobin level of 7 to 9 g/dl in patients without hypoperfusion, critical coronary artery disease or myocardial ischemia, or acute hemorrhage	1B
Infection control	
Obtain blood cultures before antibiotic therapy is administered	1C
Perform imaging studies promptly to confirm source of infection	UG
Administer broad-spectrum antibiotic therapy within 1 hr after diagnosis of either severe sepsis or septic shock	1B/1C
Reassess antibiotic therapy daily for de-escalation when appropriate	1B
Perform source control with attention to risks and benefits of the chosen method within 12 hr after diagnosis	1C
Respiratory support	
Use a low tidal volume and limitation of inspiratory-plateau-pressure strategy for ARDS	1A/1B
Apply a minimal amount of positive end-expiratory pressure in ARDS	1B
Administer higher rather than lower positive end-expiratory pressure for patients with sepsis-induced ARDS	2C
Use recruitment maneuvers in patients with severe refractory hypoxemia due to ARDS	2C
Use prone positioning in patients with sepsis-induced ARDS and a ratio of the partial pressure of arterial oxygen (mm Hg) to the fraction of inspired oxygen of <100, in facilities that have experience with such practice	2C
Elevate the head of the bed in patients undergoing mechanical ventilation, unless contraindicated	1B
Use a conservative fluid strategy for established acute lung injury or ARDS with no evidence of tissue hypoperfusion	1C
Use weaning protocols	1A

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Central nervous system support	
Use sedation protocols, targeting specific dose-escalation end points	1B
Avoid neuromuscular blockers if possible in patients without ARDS	1C
Administer a short course of a neuromuscular blocker (<48 hr) for patients with early, severe ARDS	2C
General supportive care	
Use a protocol-specified approach to blood glucose management, with the initiation of insulin after two consecutive blood glucose levels of >180 mg/dl (10 mmol/liter), targeting a blood glucose level of <180 mg/dl	1A
Use the equivalent of continuous venovenous hemofiltration or intermittent hemodialysis as needed for renal failure or fluid overload	2B
Administer prophylaxis for deep-vein thrombosis	1B
Administer stress-ulcer prophylaxis to prevent upper gastrointestinal bleeding	1B
Administer oral or enteral feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hr after a diagnosis of severe sepsis or septic shock	2C
Address goals of care, including treatment plans and end-of-life planning as appropriate	1B

* Data are adapted from Dellinger et al.[23] ARDS denotes acute respiratory distress syndrome, and ICU intensive care unit.
† For all grades, the number indicates the strength of the recommendation (1, recommended; 2, suggested), and the letter indicates the level of evidence, from high (A) to low (D), with UG indicating ungraded. Recommendations that are specific to pediatric severe sepsis include therapy with face-mask oxygen, high-flow nasal cannula oxygen, or nasopharyngeal continuous positive end-expiratory pressure in the presence of respiratory distress and hypoxemia (2C); use of physical examination therapeutic end points, such as capillary refill (2C); administration of a bolus of 20 ml of crystalloids (or albumin equivalent) per kilogram of body weight during a period of 5 to 10 minutes for hypovolemia (2C); increased use of inotropes and vasodilators in septic shock with low cardiac output associated with elevated systemic vascular resistance (2C); and use of hydrocortisone only in children with suspected or proven absolute adrenal insufficiency (2C).
‡ The guidelines recommend completing the initial fluid resuscitation within 3 hours (UG).

sion may also contribute to sepsis-associated immunosuppression.[42]

ORGAN DYSFUNCTION

Although the mechanisms that underlie organ failure in sepsis have been only partially elucidated, impaired tissue oxygenation plays a key role (Fig. 2). Several factors — including hypotension, reduced red-cell deformability, and microvascular thrombosis — contribute to diminished oxygen delivery in septic shock. Inflammation can cause dysfunction of the vascular endothelium, accompanied by cell death and loss of barrier integrity, giving rise to subcutaneous and body-cavity edema.[43] In addition, mitochondrial damage caused by oxidative stress and other mechanisms impairs cellular oxygen use.[44] Moreover, injured mitochondria release alarmins into the extracellular environment, including mitochondrial DNA and formyl peptides, which can activate neutrophils and cause further tissue injury.[45]

TREATMENT

The Surviving Sepsis Campaign, an international consortium of professional societies involved in critical care, treatment of infectious diseases, and emergency medicine, recently issued the third iteration of clinical guidelines for the management of severe sepsis and septic shock (Table 2).[23] The most important elements of the guidelines are organized into two "bundles" of care: an initial management bundle to be accomplished within 6 hours after the patient's presentation and a management bundle to be accomplished in the ICU.[23] Implementation of the bundles is associated with an improved outcome.[46,47]

The principles of the initial management bundle are to provide cardiorespiratory resuscitation and mitigate the immediate threats of uncontrolled infection. Resuscitation requires the use of intravenous fluids and vasopressors, with oxygen therapy and mechanical ventilation provided as necessary. The exact components required to optimize resuscitation, such as the choice and amount of fluids, appropriate type and intensity of hemodynamic monitoring, and role of adjunctive vasoactive agents, all remain the subject of ongoing debate and clinical trials; many of these issues will be covered in this series.[23] Nonetheless, some form of resuscitation is considered essential, and a standardized approach

has been advocated to ensure prompt, effective management.[23] The initial management of infection requires forming a probable diagnosis, obtaining cultures, and initiating appropriate and timely empirical antimicrobial therapy and source control (i.e., draining pus, if appropriate).

The choice of empirical therapy depends on the suspected site of infection, the setting in which the infection developed (i.e., home, nursing home, or hospital), medical history, and local microbial-susceptibility patterns. Inappropriate or delayed antibiotic treatment is associated with increased mortality.[48,49] Thus, intravenous antibiotic therapy should be started as early as possible and should cover all likely pathogens. It has not been determined whether combination antimicrobial therapy produces better outcomes than adequate single-agent antibiotic therapy in patients with severe sepsis.[50-53] Current guidelines recommend combination antimicrobial therapy only for neutropenic sepsis and sepsis caused by pseudomonas species. Empirical antifungal therapy should be used only in patients at high risk for invasive candidiasis.[50]

The patient should also be moved to an appropriate setting, such as an ICU, for ongoing care. After the first 6 hours, attention focuses on monitoring and support of organ function, avoidance of complications, and de-escalation of care when possible. De-escalation of initial broad-spectrum therapy may prevent the emergence of resistant organisms, minimize the risk of drug toxicity, and reduce costs, and evidence from observational studies indicates that such an approach is safe.[54] The only immunomodulatory therapy that is currently advocated is a short course of hydrocortisone (200 to 300 mg per day for up to 7 days or until vasopressor support is no longer required) for patients with refractory septic shock.[23] This recommendation is supported by a meta-analysis,[55] but the two largest studies had conflicting results,[56,57] and other clinical trials are ongoing.[58,59]

SEARCH FOR NEW THERAPIES

RECENT FAILURES

One of the great disappointments during the past 30 years has been the failure to convert advances in our understanding of the underlying biologic features of sepsis into effective new therapies.[60] Researchers have tested both highly specific agents and agents exerting more pleiotropic effects. The specific agents can be divided into those designed to interrupt the initial cytokine cascade (e.g., antilipopolysaccharide or anti–pro-inflammatory cytokine strategies) and those designed to interfere with dysregulated coagulation (e.g., antithrombin or activated protein C).[61] The only new agent that gained regulatory approval was activated protein C.[62] However, postapproval concern about the safety and efficacy of activated protein C prompted a repeat study, which did not show a benefit and led the manufacturer, Eli Lilly, to withdraw the drug from the market.[11] All other strategies thus far have not shown efficacy. With the recent decision to stop further clinical development of CytoFab, a polyclonal anti–tumor necrosis factor antibody (ClinicalTrials.gov number, NCT01145560), there are no current large-scale trials of anticytokine strategies in the treatment of sepsis.

Among the agents with broader immunomodulatory effects, glucocorticoids have received the most attention. Intravenous immune globulin is also associated with a potential benefit,[63] but important questions remain, and its use is not part of routine practice.[23] Despite a large number of observational studies suggesting that the use of statins reduces the incidence or improves the outcome of sepsis and severe infection,[64] such findings have not been confirmed in randomized, controlled trials, so the use of statins is not part of routine sepsis care.[23]

PROBLEMS WITH THERAPEUTIC DEVELOPMENT

Faced with these disappointing results, many observers question the current approach to the development of sepsis drugs. Preclinical studies commonly test drugs in young, healthy mice or rats exposed to a septic challenge (e.g., bacteria or bacterial toxins) with limited or no ancillary treatment. In contrast, patients with sepsis are often elderly or have serious coexisting illnesses, which may affect the host response and increase the risk of acute organ dysfunction. Furthermore, death in the clinical setting often occurs despite the use of antibiotics, resuscitation, and intensive life support, and the disease mechanisms in such cases are probably very different from those underlying the early deterioration that typically occurs in animal models in the absence of supportive care. There are also large between-species genetic differences in the inflammatory host response.[65]

In clinical studies, the enrollment criteria are typically very broad, the agent is administered on the basis of a standard formula for only a short period, there is little information on how the agent changes the host response and host–pathogen interactions, and the primary end point is death from any cause. Such a research strategy is probably overly simplistic in that it does not select patients who are most likely to benefit, cannot adjust therapy on the basis of the evolving host response and clinical course, and does not capture potentially important effects on nonfatal outcomes.

NEW STRATEGIES

Consequently, hope is pinned on newer so-called precision-medicine strategies with better preclinical models, more targeted drug development, and clinical trials that incorporate better patient selection, drug delivery, and outcome measurement. For example, options to enrich the preclinical portfolio include the study of animals that are more genetically diverse, are older, or have preexisting disease. Longer experiments with more advanced supportive care would allow better mimicry of the later stages of sepsis and multiorgan failure, permitting the testing of drugs in a more realistic setting and perhaps facilitating the measurement of outcomes such as cognitive and physical functioning. In addition, preclinical studies could be used to screen for potential biomarkers of a therapeutic response for which there are human homologues.

Activated protein C mutants that lack anticoagulant properties are examples of more targeted drug development and were shown to provide protection from sepsis-induced death in animals, without an increased risk of bleeding.[66] Biomarkers such as whole-genome expression patterns in peripheral-blood leukocytes may aid in stratifying patients into more homogeneous subgroups or in developing more targeted therapeutic interventions.[67] The insight that severe sepsis can cause immunosuppression raises the possibility of using immune-stimulatory therapy (e.g., interleukin-7, granulocyte–macrophage colony-stimulating factor,[68] or interferon-γ[69]), but ideally, such therapy would be used only in patients in whom immunosuppression is identified or predicted. Thus, such therapies could be deployed on the basis of laboratory measures, such as monocyte HLA-DR expression. In addition, concern about accelerated neurocognitive decline in survivors of sepsis opens up avenues to explore agents currently being tested in patients with dementia and related conditions.

The designs of trials could be modified to more easily incorporate these ideas. For example, the considerable uncertainty at the beginning of a trial with regard to the appropriate selection of patients and drug-administration strategy and the possibility of treatment interactions may be better handled with the use of a Bayesian design. A trial could commence with multiple study groups that reflect the various uncertainties to be tested but then automatically narrow assignments to the best-performing groups on the basis of predefined-response adaptive randomization rules. Such designs could be particularly helpful when testing combination therapy or incorporating potential biomarkers of drug responsiveness.

CONCLUSIONS

Severe sepsis and septic shock represent one of the oldest and most pressing problems in medicine. With advances in intensive care, increased awareness, and dissemination of evidence-based guidelines, clinicians have taken large strides in reducing the risk of imminent death associated with sepsis. However, as more patients survive sepsis, concern mounts over the lingering sequelae of what was previously a lethal event. Strategies are also needed to reach the many millions of patients with sepsis who are far from modern intensive care. At the same time, advances in molecular biology have provided keen insight into the complexity of pathogen and alarm recognition by the human host and important clues to a host response that has gone awry. However, harnessing that information to provide effective new therapies has proved to be difficult. To further improve the outcome of patients with sepsis through the development of new therapeutic agents, newer, smarter approaches to clinical-trial design and execution are essential.

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