PART II Clinical Syndromes and Cardinal Features of Infectious Diseases: Approach to Diagnosis and Initial Management

SECTION A: Septicemia, Toxin- and Inflammation-Mediated Syndromes

11 The Systemic Inflammatory Response Syndrome (SIRS), Sepsis, and Septic Shock

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Sepsis remains a major cause of morbidity and mortality among children.[1-4] Sepsis-associated mortality in children has decreased from 97% in 1966[5] to 9% among infants in the early 1990s.[6] A recent population-based study of United States children with severe septicemia (bacterial or fungal infection with at least one acute organ dysfunction) reported a mortality rate of 10.3%.[7] Although this represents a significant improvement over past decades, severe sepsis remains one of the leading causes of death in children, with over 4300 deaths annually (7% of all deaths among children) and estimated annual total costs of $1.97 billion.[8]

In a seminal study, Watson et al.[8] analyzed the impact of age, sex, birthweight, underlying disease, and microbiologic etiology on the incidence, mortality, and hospital costs of children who develop septicemia using 1995 hospital discharge and population data from seven states. Table 11-1 shows the annual incidence, case fatality, and national estimates of severe sepsis by age. The incidence is highest in infants (5.16 per 1000), falls significantly in older children (0.20 per 1000 in 10- to 14-year-olds), and also exhibits a sex difference, being 15% higher in boys than in girls (0.60 versus 0.52 per 1000, $P < 0.001$).[8] Overall hospital mortality was 10.3%, or 4383 deaths nationally (6.2 per 100,000 population).[8] Of interest, about 50% of the cases had an underlying disease and over 20% were low-birthweight neonates. The most common infections were respiratory tract (37%) and primary bloodstream infections (BSIs) (25%).[8] The mean length of hospital stay was 31 days, and the cost was $40,600 per admission.[8]

TABLE 11-1. Annual Incidence, Case Fatality, and National Estimates of Severe Sepsis by Age

Age	Incidence (Per 1000 Population)	National Estimate of Cases	Case Fatality (%)	National Estimate of Deaths
<1 year[a]	5.16	20,145	10.6	2135
0–28 days[b]	3.60	14,049	10.3	1361
29–364 days[b]	1.56	6,096	13.5	774
1–4 years[a]	0.49	7,583	10.4	786
5–9 years[a]	0.22	4,168	9.9	413
10–14 years[a]	0.20	3,836	9.6	368
15–19 years[a]	0.37	6,633	9.7	644
All children	0.56	42,364	10.3	4383

[a]*National estimates are generated from the seven-state cohort using state and national age- and sex-specific population estimates from the National Center for Health Statistics and the United States Census.*

[b]*Results for these ages are based on data from the five states (MA, MD, NJ, NY, and VA) in which neonates could be identified (n = 6349 or 66% of the entire seven-state cohort).*

From Watson RS, Carcillo JA, Linde-Zwirble WT, et al. The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med 2003;167:695–701.

DEFINITIONS

An international panel of experts in the fields of adult and pediatric septicemia and clinical research proposed the first set of specific definitions and criteria for the components of the sepsis continuum that can be applied consistently in the pediatric population in 2005.[6] These definitions were used again in the international guidelines for management of sepsis and septic shock.[9] The consensus definitions for systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome in children are listed in Box 11-1. It is important to recognize that these definitions were meant for use in the design, conduct, and analysis of large, multicenter, international therapeutic trials rather than as a clinical tool at the bedside. It is clear that, given the intra- and inter-individual differences in the time course of disease progression, these definitions often have limited clinical utility.

The diagnosis and thus the definition of septic shock in children can be challenging. Children often maintain blood pressure until severely ill;[10] while there is no requirement for systemic hypotension in order to make the diagnosis of septic shock as there is in adults, a recent expert review committee recommends early recognition of septic shock in premature neonates, infants, and children using clinical examination, not biochemical tests.[11] Shock can occur long before hypotension occurs in children. Thus, shock can be diagnosed clinically before hypotension occurs by clinical signs, which include hypothermia or hyperthermia, altered mental status, and peripheral vasodilation (warm shock) or vasoconstriction with capillary refill >2 seconds (cold shock).[11] Hypotension is a sign of late and decompensated shock in children and is confirmatory of shock state if present in a child with suspected or proven infection.[12] Although there are distinct clinical presentations and classifications of shock in children (e.g., warm and cold shock; fluid-refractory and catecholamine-resistant shock), septic shock is defined as septicemia in the presence of cardiovascular dysfunction (i.e., severe sepsis with cardiovascular dysfunction).[6]

ETIOLOGY

Several factors influence the potential pathogens causing septicemia in children, including age, host immune status, and geographic location at the time of infection. In addition, organisms causing community-onset infections differ from those acquired in the hospital setting. During the neonatal period, common bacterial causes include group B streptococci and enteric bacilli, such as *Escherichia coli*. Other less common pathogens include enterococci, *Listeria monocytogenes, Staphylococcus*

BOX 11-1. Definitions of Systemic Inflammatory Response Syndrome, Infection, Sepsis, Severe Sepsis, and Septic Shock

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

The presence of two or more of the following criteria, one of which must be abnormal temperature or leukocyte count:

- Core[a] temperature of >38.5°C *or* <36°C
- Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hour time period *or* for children <1 year old: Bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, beta-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hour time period
- Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia
- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils

INFECTION

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen *or* a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest X-ray consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)

SEPSIS

SIRS in the presence of or as a result of suspected or proven infection

SEVERE SEPSIS

Sepsis plus the following: cardiovascular organ dysfunction, acute respiratory distress syndrome (ARDS), or two or more other organ dysfunctions

SEPTIC SHOCK

Sepsis and cardiovascular organ dysfunction

[a]Core temperature must be measured by rectal, oral, or central catheter probe.

From Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8.

aureus (including methicillin-resistant *Staphylococcus aureus*) and *Streptococcus pneumoniae*. Advances in neonatology and survival of extremely- and very-low-birthweight infants affect the epidemiology of hospital-associated neonatal sepsis. The use of central venous catheters (CVCs) and other foreign bodies further predispose these already compromised neonates to pathogens such as coagulase-negative staphylococci, *S. aureus,* less common gram-negative bacilli, and *Candida* spp. Viral neonatal sepsis may be indistinguishable clinically from bacterial infection. Viral pathogens include herpes simplex virus, enteroviruses, respiratory syncytial virus, and influenza virus.

Beyond the neonatal period, *S. pneumoniae* and *Neisseria meningitidis* are common causes of sepsis in otherwise healthy children. *Haemophilus influenzae* type b (Hib) should be considered in the incompletely vaccinated child. In 2005, only 9 cases of invasive Hib disease in children <5 years of age were reported in the U.S.[13] In 2008, this increased to 30 cases.[14] Since the routine administration of the heptavalent pneumococcal conjugate vaccine in 2000, the overall incidence of invasive pneumococcal disease in children <5 years of age has declined by 76%.[15] Other organisms include *S. aureus* and *Streptococcus pyogenes* (also causing toxic shock syndrome), *Salmonella* spp., and rickettsia in certain geographic regions (Rocky Mountain spotted fever and ehrlichiosis). In hospitalized infants and children with indwelling CVCs, coagulase-negative staphylococci, *S. aureus*, gram-negative bacilli, and *Candida* spp. are important causes of sepsis due to central line associated bloodstream infection (CLABSI).

Children with underlying immunodeficiency states can develop septicemia due to the same pathogens as healthy children; however, some conditions predispose to additional organisms. Neutropenic cancer patients with mucositis are at risk of sepsis due to the Enterobacteriaceae, other gram-negative bacilli such as *Pseudomonas aeruginosa,* and alpha-hemolytic (viridans) streptococci. The last are associated with acute respiratory distress syndrome (ARDS) and can cause meningitis.[16,17] As most oncology patients have indwelling CVCs, they also remain at risk for the typical CLABSI pathogens. Other conditions increase risk of sepsis due to certain pathogens, e.g., acquired immunodeficiency virus (AIDS) for *S. pneumoniae, P. aeruginosa, S. aureus,* and Hib; anatomic or functional asplenia (including sickle-cell disease) for encapsulated organisms such as *S. pneumoniae, Salmonella* spp., Hib, and *N. meningitidis*; and cyclic neutropenia for *Clostridium* species.

PATHOPHYSIOLOGY

If a microbe gains access to the intravascular compartment, the host activates defensive mechanisms. Transient bacteremia without significant clinical consequences occurs commonly in healthy children. In others, probably depending on the age and immunocompetence of the patient, the virulence and number of pathogens in the blood, and the timing and nature of a therapeutic intervention, the host's systemic inflammatory response ensues and can progress independently, despite successful eradication of the microbe. Although infection is a major cause of the systemic inflammatory response syndrome (SIRS), a number of other entities, including trauma, ARDS, neoplasm, burn injury, pancreatitis, and dysfunctional macrophage activation, are also recognized causes.

Most pathophysiologic consequences of the sepsis syndrome result from an imbalance between pro- and anti-inflammatory mediators in combination with microbial toxins.[18] In children, severe sepsis arises from coordinated activation of the innate immune response.[19] This response, triggered by diverse pathogens, is multifaceted.[18–20] Once triggered, the response leads to secretion of pro- and anti-inflammatory cytokines, activation and mobilization of leukocytes, activation of coagulation and inhibition of fibrinolysis,[21,22] and increased apoptosis.[23] As a result of coagulation activation, thrombin generated promotes fibrin deposition in the microvasculature and also exacerbates ongoing inflammation by direct and indirect mechanisms.[18] Although evolutionarily designed to limit microbial dissemination, overexuberant innate inflammatory processes may be detrimental, resulting in cardiac dysfunction, vasodilation, capillary injury, and micro- and macrovascular thromboses. Despite antimicrobial therapy and intensive supportive care, these processes frequently lead to organ dysfunction, thrombotic complications, long-term neurologic morbidity, or death (Table 11-1).[1,24]

The clinical manifestations of sepsis are the result of systemic inflammation and include abnormal temperature regulation, flushed warm skin, widened pulse pressure, tachycardia, tachypnea, metabolic acidosis (elevated serum lactate, decreased base excess), renal and/or hepatic dysfunction, thrombocytosis, and leukocytosis. As the syndrome progresses, multiorgan failure, including acute respiratory failure, hypotension, myocardial failure, decreased neurologic function, oliguric or anuric renal failure, hepatic failure, leukopenia, anemia, and thrombocytopenia, can ensue and can lead to death.

CLINICAL AND LABORATORY FINDINGS

Fever, tachycardia, and tachypnea are the most common physiologic abnormalities associated with sepsis, even though they are insensitive and nonspecific. Other clinical signs include decreased tone, diminished activity, pale or grey skin color, prolonged capillary refill time, and poor feeding or sucking.[25] Biochemical markers of inflammation may one day prove to be more objective and reliable than physiologic findings; however, no biochemical marker has been confirmed to be robust enough to use for the definitive diagnosis of sepsis or for tracking response to therapy and disease progression. Early recognition of septic shock depends on clinical recognition, as there are no reliable biochemical tests available to date.[11] Early treatment with antibiotics and fluid resuscitation has been demonstrated clearly to reduce both morbidity and mortality.[11,12,26]

Clinical Signs

The earliest clinical sign of clinical infection is age-dependent changes in body temperature.[27] In immune-competent children the earliest sign is fever. In immune-compromised children and premature infants the earliest sign can be hypothermia or fever.[27] Fever in association with changes in a child's behavior, such as an infant's loss of smiling or playfulness (especially after fever has been controlled with antipyretic therapy), are signs of serious infection, which may benefit from antibacterial, antiviral, or antifungal therapy.[28–30]

Tachycardia is a useful sign of sepsis in the neonate born at term,[31] as is tachycardia and/or tachypnea in older children.[27] Fever can account for some tachycardia, as each 1°C increase can result in an increase in heart rate of 10%; however, the heart rate and respiratory rate should become normal for age when fever is controlled with antipyretic therapy or falls spontaneously.[27] Heart rate >150 beats/minute in children and >160 beats/minute in infants, and respiratory rates >50 breaths/minute in children and >60 breaths/minute in infants are associated with increased mortality risk and commonly presage the development of septic shock.[6] A minimum mean arterial pressure of >30 mmHg is considered absolutely the lowest tolerable blood pressure in the extremely premature infant.[11,32] Specific hemodynamic abnormalities at the time of coming to medical attention have been associated with increasing mortality: eucardia (1%), tachycardia/bradycardia (3%), hypotension with capillary refill <3 seconds (5%), normotension with capillary refill >3 seconds (7%), hypotension with capillary refill >3 seconds (33%).[11]

Laboratory Findings

Numerous biologic markers of sepsis in children have been studied; however, none has independent high positive or negative predictive value for decision making in clinical practice based on evidence of prospective clinical trials.[27,33] Biomarkers that are commonly used clinically include: the total peripheral white blood cell (WBC) count,[34,35] platelet count, erythrocyte sedimentation rate (ESR), base excess/base deficit, lactate,[36,37] procalcitonin (PCT),[38–41] C-reactive protein (CRP),[42–45] and interleukin-6 (IL-6).[41,46,47] Many tests and biologic markers currently under study and development are promising and include specific rapid antigen assays,[48] polymerase chain reaction tests,[49–51] genomic testing (for guiding therapy and determining host response),[52,53] and proteomic testing (for identification of differentially expressed proteins and peptides).[54–58] Use of combinations of tests may improve independent predictive values.[59]

MANAGEMENT

Antimicrobial Therapy

Empiric antimicrobial therapy for severe sepsis should be administered urgently, targeting likely causative pathogens (Table 11-2). Important considerations when selecting a regimen include: the child's age, community versus hospital acquisition, host immune status, and penetration into affected or at-risk tissues and compartments (such as central nervous system). In U.S. cities, as many as 76% of invasive, community-associated *S. aureus* isolates can be methicillin resistant.[60] Vancomycin should be included in the empiric regimen if *S. aureus* is suspected. Once the causative organism is isolated and antibiotic susceptibilities are available, antimicrobial therapy is adjusted appropriately. When possible, broad-spectrum agents (such as vancomycin, third-generation cephalosporins and carbapenems) should be discontinued to minimize the emergence of multidrug-resistant organisms in the patient and spread in the patient's environment. If *Escherichia coli* or *Klebsiella* spp. (or other gram-negative bacilli in certain hospital settings) are isolated, the organism is tested for extended-spectrum β-lactamase (ESBL) production. Carbapenems are the treatment of choice for serious infections with ESBL-producing organisms.[61]

TABLE 11-2. Suggested Initial Antimicrobial Choices for Empiric Therapy in Infants and Children with Suspected Sepsis[a]

Age or Clinical Situation	Antimicrobial Agent(s)
Neonate (community-onset)	Ampicillin + gentamicin
Neonate (hospital-onset)	Vancomycin + gentamicin *or* cefotaxime[b]
Child (community-onset)	Cefotaxime *or* ceftriaxone + vancomycin
Child (hospital-onset)	Vancomycin + anti-pseudomonal penicillin *or* ceftazidime *or* carbapenem[b]
Skin or soft-tissue involvement	Vancomycin *or* semi-synthetic penicillin + clindamycin
Toxic shock syndrome	Vancomycin *or* semi-synthetic penicillin + clindamycin
Neonatal HSV[c]	Acyclovir
Rocky Mountain spotted fever Ehrlichiosis	Doxycycline

[a]*Antimicrobials should be modified as laboratory data is available and based on clinical course.*

[b]*Antimicrobial should be based on patient-specific risk factors and local antimicrobial susceptibility trends (see text).*

[c]*HSV, herpes simplex virus.*

Supportive Care

Effective treatment of sepsis and septic shock is dependent on prompt recognition and initiation of supportive as well as specific therapy. The basic principles of initial critical care include ensuring adequate circulation, airway patency, and gas exchange. The interventions required to achieve these goals depend on the specific physiologic state of the patient at the time of presentation. Shock that occurs during sepsis results from decreased intravascular volume, maldistribution of intravascular volume, and/or impaired myocardial function, all of which can occur at different times during the course of septic shock.[62] Children with sepsis who receive early aggressive fluid resuscitation (>40 mL/kg in the first hour with isotonic intravenous fluids) demonstrate improved survival without increased risk of noncardiogenic pulmonary edema or ARDS.[63,64]

Determination of when, what type, and how much pharmacologic support is needed in a patient with septic shock requires careful consideration of many factors. These factors include the patient's clinical state (e.g., capillary refill time, urine output, peripheral versus core temperature gradient), information obtained from monitoring devices (heart rate, blood pressure, central venous pressure, pulmonary artery pressure, cardiac output, stroke volume, and systemic vascular resistance), and knowledge of basic drug effects (including dopamine, norepinephrine, epinephrine, and phenylephrine) in the setting of septic shock.

Septic shock causes multisystem organ dysfunction, and it is important to evaluate and treat abnormalities in other organ systems, including the kidney and gastrointestinal tract. Patients with acute renal failure may require renal replacement therapy. The gastrointestinal tract is vulnerable to disturbances such as hemorrhage, ileus, brush border atrophy, and translocation of enteric organisms into the blood. Additionally, early institution of nutritional support, particularly enteral feeding, may ameliorate gastrointestinal atrophy, bacterial translocation, and improve multiorgan function.[65]

Maintaining tight control of serum glucose has been shown to be beneficial in some studies in critically ill adult patients and is currently being evaluated in children.[66]

Endotoxin Physiology and Antiendotoxin Therapy

Endotoxin is one of the most important bacterial components contributing to the inflammatory process. Levels of endotoxin correlate directly with severity of meningococcal disease and other forms of sepsis, and with elaboration and release of inflammatory mediators. Endotoxin upregulates TNF-α, IL-1 and IL-6, complement and coagulation pathways. Endotoxin also can be found in the presence of critical illness, not related to gram-negative sepsis,[67,68] where its presence appears to be related to severity of disease and outcome. It is postulated that the presence of endotoxin in the blood in these circumstances is related to altered gut permeability.

The assumption that the inflammatory process is related to the presence of endotoxin in the bloodstream is based on the finding that the pathophysiology of gram-negative sepsis can be reproduced by administration of purified endotoxin or a variety of endotoxin-free inflammatory mediators, which are upregulated by endotoxin.

A variety of antiendotoxin strategies have been proposed in the management of severe sepsis, including agents that bind to and neutralize endotoxin, enhance endotoxin clearance, or inhibit the interaction of endotoxin with its receptors (see Table 11-3).

Cytokine Physiology and Anticytokine Therapy

Cytokines have a central role in the pathogenesis of bacterial infection and sepsis. Cytokines coordinate a wide variety of inflammatory reactions at the tissue level. The cytokine network can be divided roughly into a proinflammatory arm and an anti-inflammatory arm. Prominent proinflammatory cytokines are TNF-α and IL-1. Anti-inflammatory cytokines, of which IL-10 is a well-studied example, inhibit the synthesis of proinflammatory cytokines and exert several direct anti-inflammatory effects on different cell types. The action of proinflammatory cytokines can be further inhibited by naturally occurring soluble inhibitors, such as soluble TNF receptors type I and type II which inhibit TNF activity, soluble IL-1 receptor type II, and IL-1ra, which both inhibit IL-1 activity.

The plasma concentrations of cytokines are rapidly dynamic and vary greatly in patients with sepsis. Some patients who fulfill the clinical criteria for SIRS may not have detectable levels of proinflammatory cytokines in their circulation because they are studied late in the septic process.[69] This may explain why the cytokines TNF-α, IL-1β, IL-12, and IFN-β, which according to animal models play a central role in the pathogenesis of septic shock, are not consistently correlated with disease severity or outcome in patients with septic shock.

Infection models that use an initially localized source of infection such as pneumonia and peritonitis have suggested that proinflammatory cytokines have a crucial role in host defense against bacterial infection. Neutralization of endogenous TNF-α during murine pneumonia caused by either gram-positive or gram-negative bacteria resulted in an accelerated course of the infection, and was associated with greater outgrowth of bacteria in the lungs, and decreased survival.[70] Conversely, the elimination of IL-10 improved survival of murine pneumonia and reduced the bacterial load within the pulmonary compartment.[71] Evidence for anticytokine therapies is summarized in Table 11-3.

Immunoparalysis

Induction of anti-inflammatory pathways to inhibit excessive proinflammatory activity can be demonstrated in most patients with sepsis. This has led to the concept of "compensatory anti-inflammatory response," following SIRS in time course.[72] In addition, shortly after the onset of a septic event, a refractory state develops that is characterized by a relative inability of host inflammatory cells to respond to usual proinflammatory stimuli (such as endotoxin challenge).[73] The diminished responsiveness involves monocytes, granulocytes, and lymphocytes. Although the mechanisms that underlie immunoparalysis have not been explained completely, it is conceivable that anti-inflammatory cytokines, particularly IL-10 and transforming growth factor-β (TGF-β) are involved.

It has been proposed that immunoparalysis could contribute to the increased susceptibility to nosocomial infection and late mortality of patients who survive the acute sepsis. As a result, strategies aiming to restore immune function have been developed and evaluated partially in patients with sepsis. Cytokines are able to reverse monocyte deactivation in vitro and in animals; IFN-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been studied with the results summarized in Table 11-3.[74–76]

Arachidonic Acid Metabolism and Inhibitor Therapy

Products of the cyclooxygenase (COX) and lipooxygenase pathways of arachidonic acid metabolism include leukotrienes, prostaglandins, and thromboxane. These products appear to play a major role in diminishing systemic vascular resistance and causing platelet aggregation, membrane lysis, and increased capillary permeability, which are the hallmarks of SIRS and shock. Drugs that interfere with these pathways have been tested as treatments for sepsis and are summarized in Table 11-3.

Immune Globulin Intravenous (IGIV) Therapy

Immune globulin intravenous (IGIV), like IFN-γ and GM-CSF, can be regarded as a treatment method aimed to improve host defense. Although plasma immune globulin concentration may be reduced in patients with sepsis, the use of IGIV therapy is not supported by randomized clinical trials. Indeed, no individual well-designed trial has been undertaken in adults with sepsis. A small non-blinded study in 21 patients with streptococcal toxic shock syndrome showed a reduced mortality (6% versus 34%, P = 0.02), suggesting possible benefit in pyrogenic exotoxin-mediated shock.[77] Results of the International Neonatal Immunotherapy Study (INIS trial), which enrolled 3493 infants, are expected to be published in the near future.[78]

Corticosteroids

Since the 1960s, investigators have attempted to modulate the inflammatory response to sepsis with corticosteroids, given at doses much higher than normal physiologic concentrations. These studies failed to show a beneficial effect of glucocorticoids in patients with sepsis.[79,80] However, more recent investigations indicate that glucocorticoids in much lower doses (supposedly inducing less immunosuppressive effects) could be of benefit to patients with septic shock.

Adrenal failure is common in critical illness, particularly in vasopressor-dependent septic shock. High baseline total serum cortisol together with a low response to a corticotropin stimulation test is correlated with a poor outcome in sepsis.[81] Several studies in children and adults with septic shock have demonstrated abnormalities of control of adrenal corticosteroid secretion over the course of illness.[82,83]

Various randomized controlled trials comparing hydrocortisone to placebo have been performed in septic shock. There is general

TABLE 11-3. Evidence for Potential Therapies for Severe Sepsis and Shock

Agent	Mechanism of Action	Studies
ANTIENDOTOXIN THERAPIES		
E5	Murine monoclonal antibody against core elements of endotoxin	915 adults with confirmed gram-negative sepsis in a multicenter placebo-controlled trial; no statistical difference in mortality[96]
HA-1A	Humanized monoclonal antibody against lipid A moiety of endotoxin	621 adults with presumed gram-negative bacillary shock in placebo-controlled trial; significantly higher mortality in those treated[97,98] 269 children with meningococcal septicemia in a placebo-controlled trial; reduced mortality by 33% (nonsignificant)[99]
rBPI21	Bactericidal-permeability inducing factor (neutrophil granule protein that can neutralize endotoxin)	393 children with meningococcal septicemia in placebo-controlled trial; no statistical difference in mortality; fewer treated patients required multiple amputations (3.2% vs. 7.4%)[100]
Statin therapy[101]	Elevates HDL levels (HDL binds to and neutralizes endotoxin); modifies T-lymphocyte activity; enhances expression of endothelial nitric oxide; modulates inflammatory cell signaling and release of cytokines; has antioxidant effects	69,168 Canadian adults in matched cohort study; reduced incidence of sepsis in treated overall and in high-risk groups, i.e., those receiving corticosteroids, patients with diabetes mellitus and malignancy[102]
Plasmapheresis or exchange transfusion	Removes endotoxin and other inflammatory mediators	Anecdotal reports of good outcomes[103–110]
Polymyxin B hemoperfusion	Binds and neutralizes endotoxin	64 adults with intra-abdominal infection in randomized 2-session hemoperfusion vs. conventional therapy; reduced vasopressor requirements and reduced 28-day mortality (32% vs. 53%)[111]
ANTICYTOKINE THERAPIES		
Monoclonal antibody against TNF-α	Removes TNF-α	Pooled data from clinical trials; reduced mortality 3.5%[112]
Soluble TNF-α receptor constructs	Mops up TNF-α	Most studies failed to demonstrate an effect. One adult placebo-controlled trial showed increased mortality in patients receiving high-dose dimeric type II TNF-α receptors[113]
Afelimomab	F(ab′) 2 fragment of murine monoclonal antibody binds to TNF-α	Adults with severe infection and high IL-6 levels in multicenter trial; relative risk of death reduced 11.9% and more rapid improvement in organ dysfunction scores[114]
Recombinant IL-1ra	Inhibits IL-1 activity	Administered in continuous infusion; no reduction in mortality[115,116]
ARACHIDONIC ACID METABOLISM THERAPIES		
Ibuprofen	Inhibits cyclooxygenase pathway	455 adults with sepsis in randomized study; reduced prostaglandin I_2, thromboxane levels, and lactic acidosis; no reduction in acute respiratory distress syndrome or mortality[117] Adults with sepsis and hypothermia; reduced 30-day mortality[118]
Pentoxifylline	Inhibits phosphodiestaerase resulting in suppression of TNF-α, IL-1, and IL-10; prevents endothelial cell dysfunction; stimulates release of tissue plasminogen activator; attenuates thromboxane release	51 adults; improved scores of organ dysfunction[119] Neonatal studies; reduced all-cause mortality[120,121]
ANTICOAGULANT THERAPIES		
Recombinant tissue factor pathway inhibitor (TFPI)	Inhibits factor Xa and possibly exerts other effects on inflammatory mediators distinct from its effect on coagulation	Improved outcome in septic animals[122] Adult phase II study; trend toward reduced mortality and no increase in adverse effects[123] 1754 adults with severe sepsis in phase III multicenter study, no effect on 28-day mortality; possible benefit in subset with severe community-acquired pneumonia[124] 2100 adults with severe community-acquired pneumonia in a prospective randomized study (CAPTIVATE) to assess 28-day mortality; results pending
Antithrombin	Inhibits thrombin, factors IXa and Xa; binds to endothelial cells modulating the inflammatory response	Continuous infusion in adults with sepsis; reduced IL-6 levels and diminished CRP[125] 2314 adults with severe sepsis in randomized trial; absolute reduction in 90-day mortality of 7.6%; difference was negated in those receiving concomitant heparin for prophylaxis of deep vein thrombosis[126]
Activated protein C (aPC)	Inactivates factors Va and VIIIa	1690 adults with severe sepsis in multicenter trial; reduced 28-day mortality[127] 477 children with severe sepsis in a randomized, placebo-controlled trial; halted early for failure to demonstrate benefit in any endpoints and appearance of increased risk of hemorrhagic complications in children <60 days of age[128]

Continued

TABLE 11-3. Evidence for Potential Therapies for Severe Sepsis and Shock—cont'd

Agent	Mechanism of Action	Studies
Tissue plasminogen activator (tPA)	Inhibits intravascular thrombosis by catalyzing conversion of plasminogen to plasmin	Rescue therapy in children with meningococcal septicemia; unacceptable level of adverse events, including fatal intracranial haemorrhage[129]
THERAPIES TARGETING THE ENDOTHELIUM		
BB-882	Antagonizes platelet-activating factor (PAF activates endothelial cells and amplifies the release of inflammatory mediators)	100 adults with severe infection; no reduction in mortality and no improvement in hemodynamic or respiratory scores[130]
TCV-309	Antagonizes PAF	98 adults; reduced organ dysfunction; no effect on mortality[131]
BN52021	Antagonizes PAF	609 adults with severe sepsis; statistically insignificant reduction in mortality[132]
Platelet-activating factor acetyl-hydrolase (PAF-AH)	A secreted plasma protein that inactivates PAF and other oxidized phospholipids	127 adults with severe sepsis; reduced all-cause mortality[133] 1261 adults with severe sepsis in a multicenter, international trial; halted early for failure to demonstrate improved 28-day mortality or secondary endpoints[134]

agreement that hydrocortisone supplementation improves the hemodynamic condition of vasopressor-dependent septic shock.[84] What remains more controversial is the definition of adrenal insufficiency, the optimal dose and timing of corticosteroid supplementation, whether this should then be tapered slowly, and the impact of corticosteroid supplementation on outcome. A multicenter, randomized, placebo-controlled trial of 499 patients with septic shock[85] found that hydrocortisone did not improve overall survival or in the subgroup of patients who did not have a response to corticotropin, although shock was reversed more quickly in the hydrocortisone-treated group than in the placebo group.

Although no study has evaluated the efficacy of corticosteroids in children with sepsis, several well-designed trials conducted in children with bacterial meningitis, most of whom had bacteremia when enrolled, have shown that early administration of dexamethasone was associated with significant reduction in hemodynamic instability in the 6 hours after initiation of antibiotic therapy.[86]

Anticoagulant Therapies

Virtually all patients with sepsis have coagulation abnormalities. These abnormalities can vary from subclinical alterations in clotting times, to full-blown disseminated intravascular coagulation (DIC). Because of the recognized interactions between inflammation and coagulation, manipulation of the coagulation cascade would appear to be an attractive target for new therapies (see Table 11-3).

Therapies Targeting the Endothelium

Endothelial dysfunction appears to be pivotal as the primary pathologic feature of severe sepsis. Restoration of endothelial function by interventions to reduce endothelial cell injury and dysfunction are being developed (see Table 11-3).

Nitric Oxide Balance

Activation of the inflammatory response results in elaboration of a number of mediators with direct effects on vasomotor tone. Nitric oxide (NO), bradykinin, histamine, and prostaglandin I_2 (PGI_2) can all decrease vascular tone and cause hypotension. NO is a highly diffusible compound that activates soluble guanylate cyclase in smooth-muscle cells. This converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which relaxes the smooth-muscle cell via a protein kinase, by promoting calcium entry into the sarcoplasmic reticulum.[87]

The inflammatory response in sepsis, including increased NO production, can result in endothelial cell dysfunction affecting vascular smooth muscle. The resulting effects on organ perfusion may be instrumental in the pathogenesis of the multiple organ dysfunction syndrome seen in septic shock, which is associated with increased morbidity and mortality. The implication of NO in the vascular hyporesponsiveness and cardiac depression of sepsis supports the hypothesis that blockage or reduction of NO production may produce clinical benefit in patients with sepsis (see Table 11-3).

However, there are many animal models of sepsis in which various inhibitors of NO production have demonstrated potentially harmful effects as well as potential benefit. It has become clear, however, that nonspecific NO inhibitors cause detrimental effects secondary to reduced organ perfusion, elevation of pulmonary artery pressures, and increased renal vascular resistance[88,89] as well as increased capillary permeability, increased lactic acidosis, and hepatic toxicity.[90] This is likely to be due to inhibition of baseline NO production which is essential for control of organ perfusion under normal circumstances.

Innate Immune Responses and Toll-Like Receptors (TLRs)

The most exciting new development in sepsis research in the past years is the discovery of TLRs as signal-transducing elements of multiple antigens and the rapidly unfolding picture of TLRs as essential in the innate immune response to infection.[91]

Upon first encounter with a microorganism, the innate immune system can distinguish between different classes of pathogenic bacteria, viruses, and fungi. The innate immune system can recognize conserved motifs on pathogens that are not seen on higher eukaryotes. These motifs have been referred to as "pathogen-associated molecular patterns" or PAMPs, whereas their binding partners on immunocompetent cells have been termed "pattern recognition receptors."

Endotoxin, for example, interacts with cells via the pattern recognition receptor CD14. Spontaneous binding of endotoxin to CD14 occurs at very slow rates. Lipopolysaccharide (LPS) CD14-binding is greatly accelerated in the presence of an acute-phase reactant mainly derived from the liver, lipopolysaccharide-binding protein (LBP). CD14 does not have an intracellular domain; cells respond to endotoxin via signaling through TLR4, which requires the presence of a secreted protein, MD-2. TLR2 in turn is essential for signaling the proinflammatory effects of the bacterial lipoproteins, peptidoglycan and zymosan, whereas TLR5 mediates cellular effects induced by bacterial flagellin, and TLR9 mediates effects induced by unmethylated CpG-containing oligonucleotides present in bacterial (but not eukaryotic) DNA. Different members of the TLR family can act together in activating cells in response to pathogens; e.g., TLR2 and TLR6 cooperate in detecting certain bacterial components, including peptidoglycan.[92] The

in vivo relevance of induction of an effective innate immune response to infection has been shown with specific-TLR-deficient mice. TLR2 knockout mice are highly susceptible to infection due to gram-positive organisms, whereas TLR4 knockout mice have reduced resistance to gram-negative infection.[93]

Designing methods to neutralize microbial products or block their interaction with specific receptor on immune cells is an attractive concept. Monoclonal antibodies (IC14) against CD14 have been evaluated in phase I studies.[94,95] IC14 was shown to attenuate LPS-induced clinical symptoms and strongly inhibited LPS-induced proinflammatory cytokine release, while delaying the release of the anti-inflammatory cytokines. The results suggest that CD14 blockade with IC14 warrants further clinical investigation to determine its ability to attenuate the proinflammatory response due to infection.

FUTURE CONSIDERATIONS

The publication of the human genome will lead to advances in genomics and proteomics in the coming decade. The possibilities for individualized drug treatment of patients with sepsis, related to their genotype, may become reality. New technology may allow bedside testing of patients' genotypes or determination of protein or peptide biomarkers associated with poor outcome, to allow targeted therapy of even the sickest patients.

It is probable that many new agents will be developed based on the unraveling of the host–pathogen interaction. However, until this time we must utilize currently available therapies to the best of our knowledge. Despite huge advances, treatment of sepsis is still dependent upon administration of appropriate antibiotics, intravenous fluid support, and relatively crude methods of organ support. We can only improve upon current treatment of pediatric sepsis *after* there is agreement that properly conducted multicenter clinical trials can and must be carried out in critically ill children in order to test new therapies. To reach this goal, we should model pediatric sepsis trials after the successful clinical trial programs such as those that have so greatly improved survival from childhood cancer.

There have only been three large properly controlled phase III studies in children with sepsis, none of which has recruited adequate numbers to definitively determine efficacy. Although these and all the many adult studies except one have failed to demonstrate a significant survival advantage, there is much that can be learned from these unsuccessful studies that is relevant to the design of future sepsis trials. Children with severe sepsis and shock should be enrolled in double-blind, placebo-controlled studies to evaluate new treatments. These studies should be large enough to minimize random error and avoid type II error. Definitions for the target population should be explicit, reproducible, and include illness severity scores. Protocols for both the use of the investigational agent and conventional treatment should be standardized. Outcomes should be clinically relevant and predefined, and should include measures of both benefit and harm. In addition, the analysis of results should be carried out, both on evaluable patients and on the intent-to-treat population. Finally, a health economic evaluation of the implications of the introduction of ever-increasingly expensive therapies should be mandatory. Only in this way will we be likely to influence the unacceptably high mortality rate of severe sepsis in children, with the added advantage of limiting the widespread use of extremely expensive new therapies that have been insufficiently evaluated.

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