The American Journal of Medicine (2007) 120, 1012-1022

ELSEVIER

THE AMERICAN JOURNAL of MEDICINE®

REVIEW

# Sepsis

**James M. O'Brien, Jr, MD, MSc,[a] Naeem A. Ali, MD,[a] Scott K. Aberegg, MD, MPH,[a] Edward Abraham, MD[b]**

*[a]Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, The Ohio State University Medical Center, Columbus; [b]Department of Medicine, University of Alabama at Birmingham School of Medicine, Birmingham*

**ABSTRACT**

Sepsis is a clinical syndrome defined by a systemic response to infection. With progression to sepsis-associated organ failure (ie, severe sepsis) or hypotension (ie, septic shock) mortality increases. Sepsis is a cause of considerable mortality, morbidity, cost, and health care utilization. Abnormalities in the inflammation, immune, coagulation, oxygen delivery, and utilization pathways play a role in organ dysfunction and death. Early identification of septic patients allows for evidence-based interventions, such as prompt antibiotics, goal-directed resuscitation, and activated protein C. Appropriate care for sepsis may be more easily delivered by dividing this clinical entity into various stages and with changes in structures of delivery that extend across traditional boundaries. Better description of the molecular basis of the disease process also will allow for more targeted therapies. 

**KEYWORDS:** Critical care; Multi-organ failure syndrome; Sepsis; Septic shock; Severe sepsis

Despite the frequency, mortality, morbidity, and cost of sepsis, explicit patient phenotypes are lacking. Sepsis is defined by nonspecific clinical criteria that do not discriminate differences in underlying pathophysiological mechanisms. With recognition of the major public health implications and resource utilization associated with the syndrome, there is a growing awareness of sepsis and a need for an organized approach to caring for affected patients that crosses traditional structures of care.

## DEFINING A SYNDROME

Before 1992, the terminology used to define the systemic response to infection varied widely. To standardize nomenclature, a consensus conference defined sepsis as a systemic inflammatory response syndrome due to presumed or confirmed infection (Table 1).[1] The description of severe sepsis and septic shock outlined an increasingly severe spectrum of the response to infection. Subsequent studies validated that sepsis-induced organ dysfunction and shock are markers of higher mortality.[2,3]

In 2001, the participants of a second consensus conference anticipated that the definition of sepsis would evolve to one based on biological markers.[4] However, it was recognized that the previous definitions had proven useful for clinicians and researchers. Although existing definitions were overly sensitive and nonspecific, there were not sufficient data to provide compelling reasons for alternative definitions. A categorization inspired by the TNM (tumor, nodes, metastasis) staging of cancer was proposed for consideration. While this framework might better classify septic patients by pathophysiology and risk of death, it has not been validated for clinical use.

## BURDEN OF SEPSIS

There are approximately 750,000 cases of sepsis in the US annually.[5,6] Sepsis is involved in approximately 2% of all hospitalizations, and there will be more than 1 million cases of sepsis per year in the US by 2020. Hospital mortality for sepsis patients ranges from 18% to 30%, depending on the series. While the mortality rate has decreased over the past 20 years, an increase in the number of sepsis cases has resulted in a tripling of the number of sepsis-related deaths. An estimated 215,000 deaths (9.3% of all deaths) in the US occurred in patients with sepsis. In the US, care for septic patients results in hospital costs exceeding $16 billion, re-

Requests for reprints should be addressed to James M. O'Brien, Jr., MD, MSc, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, The Ohio State University Medical Center, 201 Davis HLRI, 473 12th Avenue, Columbus, OH 43210.

E-mail address: james.obrien@osumc.edu

0002-9343/$ -see front matter 
doi:10.1016/j.amjmed.2007.01.035

quires an average of 20 hospital days, and involves intensive care unit (ICU) admission in more than half of the cases. Reported costs do not include posthospitalization care or indirect costs due to delay in functional recovery. These costs may be considerable, because almost one third of survivors require intermediate care.[5]

## CLINICAL RISK FACTORS FOR SEPSIS

A number of clinical risk factors for sepsis have been identified (Table 2).[5,7-13] Causal mechanisms have not been clearly defined, and some of these factors may not have an independent association with sepsis but rather may represent other unmeasured covariates. While bacteria are often considered the sole causative agents, any microorganism can cause sepsis, including fungi, parasites, and viruses. Respiratory and intra-abdominal infections are the most common associated sites of infection.[6] Gram-positive now outnumber Gram-negative organisms as causes of sepsis. Cases of fungal infection leading to sepsis are increasing rapidly and cause up to 15% of cases.[5] In a sizeable minority of patients with the clinical presentation of sepsis, no causative organisms are found.[14] However, if infection is the suspected cause of systemic inflammatory response syndrome, the patient should be considered septic despite negative culture results, and appropriate antisepsis therapy should be instituted.

**Table 1** Consensus Conference Definitions of Systemic Inflammatory Response Syndrome, Sepsis, Severe Sepsis and Septic Shock

| Syndrome | Definition |
|---|---|
| Systemic inflammatory response syndrome | 2 or more of the following:<br>Temperature >38°C (100.4°F) or <36°C (96.8°F)<br>Pulse >90 beats per minute<br>Respiratory rate >20 breaths per minute or $PaCO_2$ <32 mm Hg<br>White blood cells >12,000/$mm^3$ or <4000/mm3 or >10% immature ("band") forms |
| Sepsis | SIRS due to suspected or confirmed infection |
| Severe sepsis | Sepsis associated with organ dysfunction, hypoperfusion or hypotension |
| Septic shock | Sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities |

## CLINICAL SIGNIFICANCE

- Sepsis accounts for 9% of all deaths in the US.
- The clinical criteria for sepsis do not discriminate differences in underlying pathophysiology, hindering development and application of effective therapies.
- An organized, multidisciplinary approach to sepsis care might improve outcomes and provide greater benefit than new therapeutic agents.
- Evidence-based treatment of sepsis includes prompt antimicrobial therapy, early resuscitation, activated protein C, and other interventions as appropriate.

## PATHOGENESIS

Because sepsis is defined as a syndrome, it is likely that heterogeneous pathophysiologic processes are contained under this single term. The interaction of microbiological products with a host that is susceptible due to genetic or other factors induces a cascade of immunomodulatory mediators, leading to cellular and organ dysfunction. The major pathways involved in sepsis include the innate immune response, inflammatory cascades, procoagulant and antifibrinolytic pathways, alterations in cellular metabolism and signaling, and acquired immune dysfunction. A full review of the pathophysiology of sepsis is beyond the scope of the current review, but several recent sources are available.[15-17]

### Immunity and Inflammation

Toll-like receptors are a class of pattern recognition molecules on immune and other cells that respond to the presence of microbiological products as part of innate immunity.[17-19] This class of receptors has a wide variety of functions,[20] but in the context of sepsis, a major outcome of Toll-like receptor engagement is the induction of pro-inflammatory mediators and activation of nuclear factor-$\kappa$B (NF-$\kappa$B).[21-23] NF-$\kappa$B is integrally involved in a cascade formerly known as "cytokine storm" associated with increased expression of proinflammatory cytokines, such as interleukin-1$\beta$ and tumor necrosis factor-$\alpha$. Other receptors, including those for complement, coagulation factors, and leukotrienes, augment and modify the Toll-like receptor-associated response.[24-27] Leukocytes are activated and recruited to the tissues directly affected by infection as well as those of distant organs. Adhesion molecules are expressed on the endothelium and participate in the recruitment of immune cells.[28,29] The complement cascade is activated in sepsis with effects on inflammation and coagulation.[30] Inducible nitric oxide synthase is up-regulated, leading to nitric oxide release, smooth muscle relaxation, local vasodilation, and systemic vasodilation.[31,32] While pro-inflammatory mediators predominate in the first few hours after sepsis onset, an anti-inflammatory reaction, including release of cytokines, such as interleukin-10, follows.[33] Within 24 hours of sepsis onset, abnormalities in coagulation and

**Table 2** Reported Association of Clinical Risk Factors with Sepsis and Severe Sepsis

| Risk Factor | Description | Odds or Risk (95% CI) |
|---|---|---|
| Demographics | | |
| Age[7] | Greater than 65 years vs ≤65 years | 13.1 (12.6 to 13.6)* |
| Race[5] | African American vs Caucasian | 1.9 (1.8 to 2.0)* |
| | Other non-Caucasian race vs Caucasian | 1.9 (1.8 to 2.0)* |
| Sex[5] | Male vs. female | 1.3 (1.2 to 1.3)* |
| Co-morbidities | | |
| HIV[10] | HIV vs no HIV | 5.1 (1.2 to 21.2)† |
| Cancer[8] | Any cancer vs no cancer | 2.8 (2.8 to 2.8)* |
| | Solid tumor vs no cancer | 1.8 (1.8 to 18.2)* |
| | Hematologic cancer vs no cancer | 15.7 (15.6 to 15.9)* |
| Cirrhosis[9] | Cirrhosis vs no cirrhosis | 2.6 (1.9 to 3.3)* |
| Alcohol dependence[13] | Ongoing alcoholism or alcohol withdrawal vs no alcohol dependence | 1.5 (1.2 to 1.9) |
| Complications of medical care | | |
| Venous access devices[12] | Central venous catheter vs peripheral venous catheter | 64 (54 to 76)* |
| Transfusion[11] | Packed red cell transfusion vs no transfusion | 6.0 (4.0 to 9.2)† |

95% CI = 95% confidence interval; HIV = human immunodeficiency virus.
*Relative risk.
†Odds ratio.

release of proinflammatory late mediators, such as high-mobility group box-1, are found.[17,34]

## Coagulation Abnormalities

Pro-inflammatory cytokines and complement activate the coagulation cascade in septic patients.[35,36] Tissue factor is expressed on immune and endothelial cells, contributing to the activation of the extrinsic coagulation system pathway that results in conversion of factor VII to an active protease.[37] Proinflammatory molecules and the interaction of Toll-like receptors with microbial products up-regulate expression of plasminogen activator inhibitor-1 (PAI-1).[38-40] Such events produce an initial activation of endothelial cells, coagulation, and fibrinolysis followed by a prolonged suppression of fibrinolysis as PAI-1 levels increase. An imbalance toward a procoagulant state results, especially in the micro-circulation.[15,41,42] Decreases in endogenous anticoagulants, including protein C, tissue factor pathway inhibitor, and antithrombin, coupled with elevated circulating and tissue levels of PAI-1, are observed in the majority of septic patients.[15] Components of the coagulation and fibrinolytic system, particularly PAI-1 and urokinase, are elevated for prolonged periods in septic patients and have substantial proinflammatory effects that may contribute to organ dysfunction.[43,44]

## Cellular Metabolism

Abnormalities in lipid, carbohydrate, and protein metabolism occur in septic patients.[45-48] Inadequate oxygen delivery due to alterations in capillary blood flow and decreased cardiac output may contribute to increased anaerobic metabolism and lactate production.[49] However, even in the presence of adequate tissue oxygen delivery, sepsis may cause impaired cellular oxygen extraction and utilization due to mitochondrial dysfunction. Sepsis-associated inhibition of cellular oxygen utilization and other metabolic pathways may lead to decreased production of oxygen radicals by some populations of dysfunctional cells.[50] This cellular "hibernation" may explain the absence of cell necrosis when failing organs from fatal cases of sepsis are examined.[51]

## Immunosuppression and Depletion

Circulating monocytes, but not neutrophils, from septic patients are hyporesponsive to proinflammatory stimuli when compared with normal cells.[52] Additionally, there is increased apoptosis of circulating lymphocyte and splenic dendritic cells in patients dying of severe sepsis.[53] This may contribute to mortality because inhibition of lymphocyte apoptosis through over-expression of anti-apoptotic molecules, such as Bcl-2, results in improved survival in experimental models.[54,55] Enhanced apoptosis of lymphoid cell populations, as well as diminished monocyte response, may increase the risk of nosocomial infections, a cause of considerable mortality in critically ill patients who survive their initial septic episode. Enhanced sepsis-induced apoptosis also may play a role in the loss of cells in the gastrointestinal and respiratory tract.[56,57] While apoptosis may be adaptive to repair damaged tissues, increased cellular apoptosis also may contribute to organ dysfunction and immunosuppression in sepsis.[53]

# RECOGNITION AND TREATMENT

Septic patients present with a variety of signs and symptoms, and recognition requires consideration of the diagnosis. Sepsis may occur in ambulatory offices, at extended care facilities, in emergency departments, on the general ward, or in the ICU. Structures and processes of care should be considered that extend beyond traditional borders within the health care continuum. As is encouraged in the care of

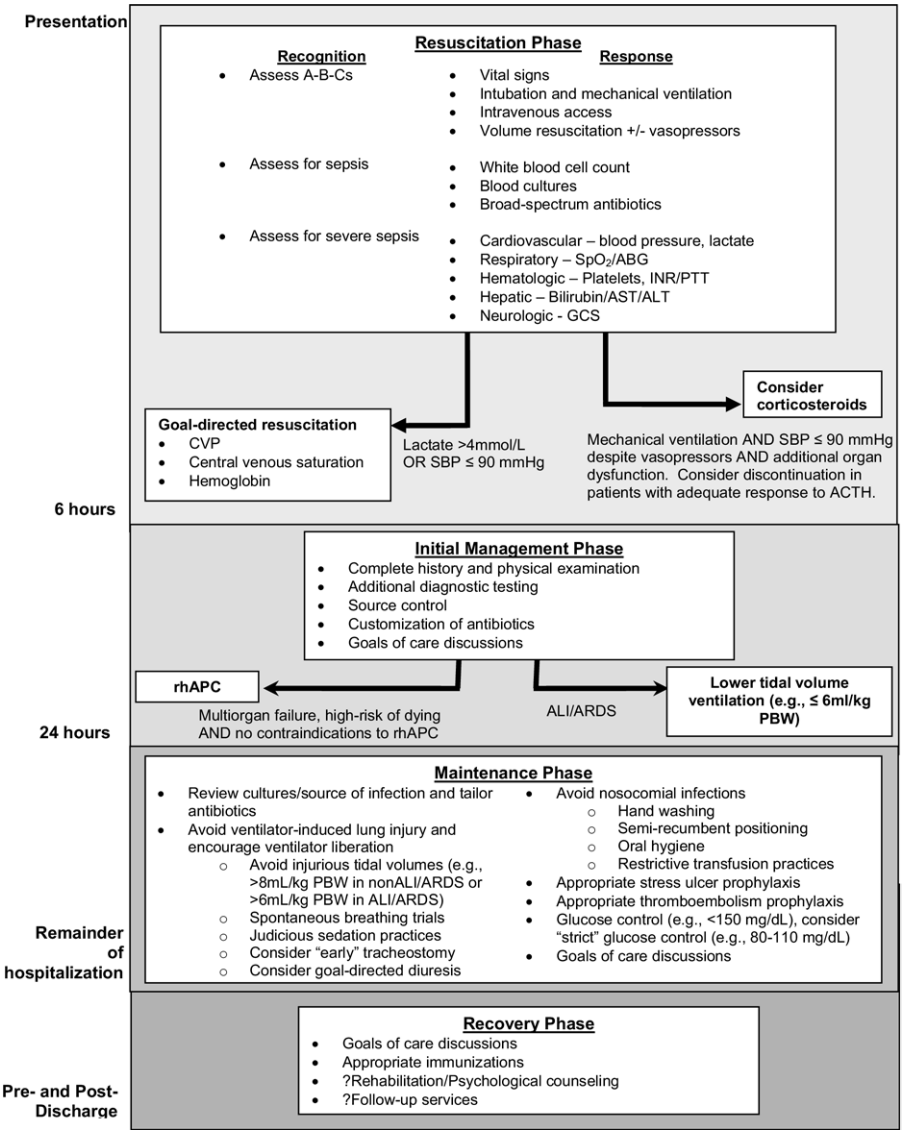


**Figure** Stages of the recognition and treatment of sepsis. Each phase should be completed within the interval listed along the left side of the figure. Selected elements of care should be delivered more rapidly than indicated in the figure (eg, antibiotic administration should occur within at least 2 hours of presentation). Patients with suspected infection should be assessed for the need for immediate resuscitative efforts. In those with the systemic inflammatory response syndrome (SIRS), an assessment for sepsis should occur with vital signs and white blood cell count. Those with SIRS and a presumed or confirmed infection should be recognized as septic and immediately proceed to the Resuscitation Phase. This includes therapeutic measures and further evaluation for evidence of severe sepsis. This phase should be completed within 6 hours. The Initial Management Phase follows and should be completed within 24 hours. The Maintenance Phase extends for the remainder of the hospitalization and the Recovery Phase may begin following initial stabilization. A-B-Cs = airway-breathing-circulation; $SpO_2$ = pulse oximetry; ABG = arterial blood gas; INR = international normalized ratio; PTT = partial thromboplastin time; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GCS = Glasgow Coma Scale score; CVP = central venous pressure; SBP = systolic blood pressure; ACTH = corticotrophin; rhAPC = recombinant human activated protein C; ALI/ARDS = acute lung injury/acute respiratory distress syndrome; PBW = predicted body weight.

patients with myocardial infarction, care may be divided into different stages based on effectiveness and urgency. Early emphasis in myocardial infarction patients is on hemodynamic stabilization and opening of the occluded vessel. Focus then shifts to secondary prevention, recovery, and rehabilitation. Various studies suggest that an approach to sepsis centered on a similar organized approach to septic patients, involving "bundles" of care, might improve outcome.[58,59]

## Recognition

To activate a therapeutic pathway (Figure), the clinician must recognize patients with a qualifying diagnosis. All patients with a suspected infection should have vital signs and a white blood cell count, and differential measured as soon as possible. A search for sepsis-induced organ dysfunction (Table 3) should follow rapidly (eg, within 2 hours) to identify severe sepsis, patients at increased risk of death,

**Table 3** Measures of Sepsis-induced Organ Dysfunction

| Organ System | Measures of Dysfunction |
|---|---|
| Cardiovascular | Low systolic arterial blood pressure, low mean blood pressure, mottled extremities, delayed capillary refill time, low cardiac output, low central or mixed venous oxygen saturations |
| Respiratory | Need for mechanical ventilation, $PaO_2/FiO_2$ ratio <300, chest radiograph abnormalities, high plateau airway pressure, low static compliance |
| Coagulation | Elevated INR, elevated PTT, elevated D-dimer, low platelets, disseminated intravascular coagulation |
| Renal | Low urine output, elevated creatinine, need for renal replacement therapy |
| Hepatic | Elevated transaminases, elevated bilirubin |
| Neurologic | Decreased mental status (eg, low Glasgow coma scale), delirium (eg, positive Confusion Assessment Method for the ICU) |
| Metabolic acidosis | Elevated lactate, elevated base deficit, low pH |
| Gastrointestinal | Ilieus |

$PaO_2$ = Partial pressure of oxygen in arterial blood; $FiO_2$ = inspired fraction of oxygen; INR = International Normalized Ratio; PTT = partial thromboplastin time; ICU = intensive care unit.

and candidates for specific therapies. Initial treatment should proceed in concert with evaluation for organ dysfunction. Because the incidence of sepsis in patients is high and specific treatment exists, it is favorable to err on the side of initial over-diagnosis.

## Resuscitation Phase

The earliest goals are to assess and secure the airway, to provide adequate volume resuscitation, and to administer appropriate antimicrobial therapy. In patients with respiratory or hemodynamic compromise, life-sustaining efforts are the first priority. In all patients, obtaining appropriate cultures and immediate administration of broad-spectrum antimicrobials should be included in the initial approach. Delayed administration of appropriate antimicrobials is associated with poorer outcomes.[60] Choices of agents should be guided by suspected site of infection, anticipated pathogens, penetration of adequate levels into infected tissues, and local patterns of antibiotic susceptibility (Table 4).

Early intervention is particularly beneficial for patients with septic shock or evidence of organ hypoperfusion (eg, elevated serum lactate levels, diminished urine output, or hypoxemia). Intubation and mechanical ventilation is recommended for patients with respiratory compromise to maintain oxygenation and acid-base status, and to mitigate diversion of the compromised circulation to the respiratory muscles. The value of rapid resuscitation directed by objective measures is illustrated by reduced observed mortality in the experimental group of a study among septic patients presenting to an emergency department.[61] The protocol included continuous measurement of central venous oxygen saturation as a measure of oxygen delivery-extraction balance, and used fluids, vasopressors, red blood cell transfusions, and inotrope therapy for 6 hours after identification of hypotension (systolic blood pressure ≤90 mm Hg) or elevated serum lactate (>4 mmol/L). Other studies of early resuscitative interventions support the findings of this single-center study.[62,63] The superiority of a particular protocol remains to be established and is being examined in a multicentered National Institutes of Health-funded study.

A central venous catheter is often necessary for diagnostic and therapeutic purposes. Subclavian and internal jugular catheters provide advantages over femoral catheters in monitoring capabilities and in reducing infectious and thrombotic complications.[64] There are few data to support the superiority of use of crystalloid or colloid solutions for resuscitation.[65] Different catecholamine vasopressor agents have not been compared in large studies, but observational and hemodynamic studies suggest that norepinephrine may be preferred.[66,67] Vasopressin, a noncatecholamine vasopressor, currently lacks compelling data to endorse its routine use.[15]

Routine corticosteroid replacement in septic shock for critical illness-related corticosteroid insufficiency remains controversial. An inadequate response to synthetic corticotrophin (ACTH; defined as ≤9 mg/dL increase in cortisol level 1 hour after administration of 250 μg ACTH) is present in the majority of patients with septic shock.[68] For septic patients with hypotension unresponsive to fluids, requirement for mechanical ventilation, and the presence of an additional sepsis-associated organ failure, administration of low doses of corticosteroids improved mortality in patients with inadequate responses to ACTH but not in those with normal responses.[69] In this study, the average time to treatment was approximately 7 hours after shock onset. Because of difficulties in determining ACTH responsiveness within this interval, a reasonable course is to perform an ACTH stimulation test and start corticosteroid treatment only in those with vasopressor-dependent shock, respiratory failure, and an additional organ failure as soon as possible after onset. Corticosteroids can be discontinued in patients with an adequate response to ACTH.

## Initial Management Phase

Following the resuscitation phase of sepsis, treatment shifts to consolidation of care. Further diagnostic testing to detect likely pathogens and sites of infection may be appropriate. Control of the source of infection, including the removal of indwelling catheters, drainage of collections of pus, and surgical debridement, may be needed. Discussions about

**Table 4** Reasonable Initial Antibiotic Choices for Sepsis, Based on Suspected Source and Likely Pathogens

| Suspected Source of Infection | Clinical Syndrome | Most Likely Pathogens | Reasonable Initial Empiric Antibiotic Agents | Comments |
|---|---|---|---|---|
| Lungs | Community-acquired pneumonia | *Streptococcus pneumoniae, Haemophilus influenzae, Legionella pneumophilia* | Third generation cephalosporin (eg, ceftriaxone) PLUS Macrolide (eg, azithromycin) OR Respiratory flouroquinlone (eg, moxifloxacin) | Consider community acquired methicillin-resistant *Staphylococcus aureus* (MRSA) depending upon local epidemiology |
| | | Influenza A and B | Oseltamivir | Consider *Staphylococcus aureus* superinfection |
| | Health-care-associated pneumonia | Gram-negative enteric bacilli, *S aureus*, *P. aureginosa* | Extended spectrum penicillin plus beta-lactamase inhibitor (eg, piperacillin/tazobactam) OR 4th generation cephalosporin (eg, cefepime) OR Carbapenem (eg, imipenem) PLUS Vancomycin | Consider second agent for Gram-negative organisms (eg, aminoglycoside) based on local patterns of susceptibility<br>Vancomycin may be dropped if low local rates of methicillin-resistant organisms |
| | Immunocompromised or Immunosuppressed patient | *Pneumocystis jiroveci* | Trimethoprim-sulfamethoxazole | HIV infection known or suspected, chronic corticosteroid use |
| | | *Aspergillus*, mucormycosis, *Histoplasmosis*, *Cryptococcosis*, *Coccioidomycosis* | Amphotericin B OR Voriconazole OR Caspofungin | Cryptococcus species are not susceptible to caspofungin |
| | | *Mycobacterium tuberculosis* | 3 or 4 drug antituberculous therapy (depending on local epidemiology) | |
| | Complicated parapnuemonic effusion | Polymycrobial infections, *S. pneumoniae*, *Streptococcal* species, *S. aureus*, Gram-negative enteric bacilli | Extended spectrum penicillin plus beta-lactamase inhibitor | Diagnostic thoracentesis for parapneumonic effusions; Thoracostomy tube drainage |
| | Lung abscess | Anaerobes; gram positive cocci | Clindamycin | |
| Bloodstream | Bacteremia without apparent source | Gram-positive cocci and Gram-negative bacilli | Carbepenem OR 3rd- or 4th-generation cephalosporin OR Extended spectrum penicillin plus beta-lactamase inhibitor ± Vancomycin or oxazolidinones (eg, linezolid) or streptogramins (eg, quinupristin/dalfopristin) | Consider endocarditis, epidural abcess, osteomyelitis, intraabdominal process |

**Table 4** Continued

| Suspected Source of Infection | Clinical Syndrome | Most Likely Pathogens | Reasonable Initial Empiric Antibiotic Agents | Comments |
|---|---|---|---|---|
| | Secondary bacteremia (indwelling venous catheter, intravenous drug user, etc.) | *Staphylococcus epidermiditis, S. aureus*, gram negative enteric bacilli | Carbepenem OR 3rd- or 4th-generation cephalosporin OR Extended spectrum penicillin plus beta-lactamase inhibitor PLUS Vancomycin or oxazolidinones or streptogranins | Consider remote seeding of infection, eg, epidural abscess Consider second agent for Gram-negative organisms (eg, aminoglycoside) based on local patterns of susceptibility |
| | High risk of fungemia | *C. albicans*, non-*albicans Candidal* species | Appropriate antibacterial antibiotics PLUS Azoles or Echinocandins or lipid formulations of Amphotericin B | Consider in patients with prior broad-spectrum antibiotics, *Candida* colonization at multiple sites, damaged physiological barriers, total parenteral nutrition, vascular access devices, immunosuppression |
| | Suspected endocarditis | *Streptococcal* species, *Enterococcal* species, *Staphylococcal* species, Gram-negative enteric bacilli, *Candida* species | Vancomycin ± Extended-spectrum penicillin (eg, piperacillin) | Consider remote seeding of infection, eg, epidural abscess |
| Skin and soft tissue infections | Cellulitis, fasciitis, myositis, osteomyelitis in normal host | *Streptococcal* species (esp Group A), *S. aureus*, anaerobes | Vancomycin ± Clindamycin | Debridement; early surgical consultation if there are concerns for necrotizing fasciitis; consider community-acquired methicillin-resistant *S. aureus* depending upon local epidemiology |
| | Cellulitis, fasciitis, myositis, osteomyelitis in patient with diabetes, peripheral vascular disease, compromised immune status | In addition to above: Gram-negative enteric bacilli, polymicrobial infection, *Pseudomonas aureginosa* | Vancomycin PLUS Extended spectrum penicillin plus beta-lactamase inhibitor ± Clindamycin | |
| | Toxic shock syndrome | *Streptococcus pyogenes*, *Staphylococcus aureus* | Clindamycin OR Aminoglycoside PLUS Nafcillin OR Vancomycin | Consider intravenous immunoglobulin |
| Genitourinary tract | Cystitis, pyelonephritis | *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* species, *Proteus* species, *Staphylococcus saprophyticus* | 4th generation cephalosporin ± Aminoglycoside | Percutaneous or transurethral drainage may be required if obstructed |
| | Puerperal sepsis | Group B beta hemolytic streptococci, Gram-negative enteric bacilli, anaerobes | Extended spectrum penicillin plus beta-lactamase inhibitor ± Aminoglycoside | |

**Table 4** Continued

| Suspected Source of Infection | Clinical Syndrome | Most Likely Pathogens | Reasonable Initial Empiric Antibiotic Agents | Comments |
|---|---|---|---|---|
| Central nervous system | Meningitis, encephalitis, intracranial abcess | *S. pneumoniae*, *Neisseria meningiditis*, *Listeria monocytogenes*, Gram-negative bacilli, *Haemophilus influenzae* | Ceftraixone OR cefotaxime ± Ampicillin (if age >60 years or impaired cellular immunity) ± Vancomycin (if recent neurosurgical procedures or high rates of penicillin-resistant *S. pneumoniae* in community) | Empiric treatment should not be delayed while awaiting lumbar puncture or laboratory results; consider dexamethasone; consider acyclovir if Herpes Simplex encephalitis considered |
| Intra-abdominal infections | Cholecystitis, cholangitis, pancreatic abcess, appendicitis, diverticulitis/ abcess, pyogenic liver abcess, perforated viscus with secondary peritonitis | *E. coli*, *K. pneumoniae*, *Bacteroides fragilis, C. albicans* | Extended spectrum penicillin plus beta-lactamase inhibitor OR Carbapenem | Early surgical consultation for open or percutaneous drainage, as indicated |
| | Spontaneous bacterial periotonitis | Gram-negative enteric bacilli, Gram-positive cocci | Cefotaxime + albumin (1.5 g/kg on day 1 and 1 g/kg on day 3) | |
| | Peritonitis associated with peritoneal dialysis | Gram-positive cocci and Gram-negative bacilli | Third generation cephalosporin PLUS Vancomycin | Intraperitoneal therapy preferred, if possible |
| | Antibiotic-associated colitis | *Clostridium difficile* | Metronidazole | Surgical consultation of signs of perforation or peritonitis |
| Other infections | Febrile neutropenia | Aerobic Gram-negative bacilli, Gram-positive cocci | Extended spectrum penicillin OR Carbapenem OR 4th generation cephalosporin PLUS Vancomycin ± Aminoglycoside ± Azole or caspofungin | |
| | Asplenic patients (eg, status-post surgical splenectomy, sickle cell anemia) | *S. pneumoniae*, *N. meningiditis, H. influenzae*, *Salmonella typhi* | Vancomycin PLUS Ceftriaxone OR Cefotaxime PLUS Aminoglycoside | Post-splenectomy syndrome (PSS) is often rapidly fatal |
| | Zoonoses, biowarfare agents, and other rare infections | *Yersinia pestis* (plague), tularemia, *Vibrio vulnificus* and *parahemolyticus*, hantavirus cardiopulmonary syndrome, ehrlichiosis, rickettsial infections, anthrax, *Strongyloides* and other parasitic infections | Varies depending upon organism doxycycline often included in empiric regimens if a zoonosis is suspected | To be considered in appropriate settings; many infections are endemic; diagnosis frequently missed or delayed |

likely prognosis and goals of care with the patient and family are appropriate considering the considerable mortality and morbidity attributable to sepsis.

For severe sepsis patients at a high risk of death, such as those with multiorgan failure or elevated severity of illness (eg, APACHE II score ≥25), drotrecogin alfa (activated) (recombinant activated protein C) should be administered if there are no contraindications.[70] The most significant side effect of this agent is bleeding. Patients at greatest risk of bleeding are those with severe thrombocytopenia, coagulopathy, or an increased risk of intracranial bleeding. For patients with high risk of death and without such contraindications, the risk of bleeding is counterbalanced by an absolute reduction in mortality. Drotrecogin alfa (activated) does not appear to be effective in patients at a low risk of death and may be harmful in those with recent surgery and single organ dysfunction.[71]

A considerable number of severe sepsis patients will develop acute lung injury. In these patients, lower tidal volumes (eg, 6 mL/kg predicted body weight) and maintenance of plateau airway pressure below 30 $cmH_2O$ improves mortality and organ failure, compared with traditional larger tidal volumes.[72] For mechanically ventilated septic patients without lung injury, lower tidal volume ventilation may prevent its development.[73] Recent studies have not shown benefit from the routine use of pulmonary artery catheters in patients with acute lung injury,[74] but have demonstrated diminished time on the ventilator with a conservative fluid strategy (eg, keeping central venous pressures <4 mm Hg).[75] Such a strategy was restricted to patients without shock or other signs of inadequate organ perfusion.

## Maintenance Phase

For septic patients surviving 24 hours, attention should turn to preventing nosocomial complications and restoring premorbid functioning. As cultures are available, antimicrobial choices, doses, and durations of therapy should be customized. Hyperglycemia is a common occurrence in critically ill patients and, in select populations, particularly postoperative patients, strict control (eg, maintenance of serum glucose at 80-110 mg/dL) may provide benefit by reducing nosocomial infections and improving survival.[76] The effectiveness of such therapy in patients with sepsis or in medical intensive care units is not proven and risks of hypoglycemia should be carefully considered.[77] Anemia occurs frequently in critically ill patients, but transfusions (after the initial resuscitation phase) may be harmful, particularly by increasing the risk of nosocomial infections.[78] Among nonbleeding patients, hemoglobin values as low as 7 mg/dL are acceptable, and there is no apparent benefit for maintaining higher levels with transfusion.[79] Avoidance of nosocomial complications also may be reduced in selected patients with the use of semi-recumbent positioning,[80] stress ulcer prophylaxis,[81] thromboembolism prophylaxis,[82] and close attention to hand-washing.[83]

As the patient stabilizes, de-escalation of invasive monitoring and life support is indicated. Liberation from mechanical ventilation at the earliest appropriate time reduces the risk of ventilator-associated complications. Judicious sedation, including daily "holidays" from sedatives, can reduce the number of ventilator and ICU days.[84] Assessment of readiness for liberation from the ventilator with spontaneous breathing trials triggered by protocols based on patient recovery, rather than physician discretion, reduces mechanical ventilation time.[85] In patients expected to require prolonged mechanical ventilation, early tracheostomy may reduce mortality, length of stay, and infectious complications.[86]

## Recovery Phase

Mortality for sepsis survivors is higher than age-matched controls for at least 5 years.[87] The mechanism of this effect is unknown. Additionally, survivors of critical illness may suffer considerable physical and psychological morbidity.[88] Small interventional studies utilizing ICU follow-up clinics and patient education initiatives following critical care demonstrate variable results.[89,90]

# CONCLUSION

Sepsis is a major cause of mortality and morbidity, and is a source of substantial health care costs. The current definition provides easy identification of affected patients but, because of the heterogeneity of patients included, may have hampered the ability to develop effective therapies and to better classify disease. Other areas of medicine, such as oncology, have learned the value in greater description of disease based on biological mechanisms for prognostic and therapeutic purposes.[91-93] It is likely that therapeutic advances in preventing and treating sepsis will be facilitated by such an approach.[94]

Sepsis is a condition that involves health care providers from many disciplines and in a variety of settings. As a result, organization of therapeutic efforts for these patients requires coordination across traditional boundaries of medicine. A concerted, multidisciplinary approach to sepsis based on patient needs, rather than physical location, may provide greater benefit than new therapeutic agents.

## References

1. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992; 101(6):1644-1655.
2. Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med*. 1995;23(10):1638-1652.
3. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-710.
4. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250-1256.

5. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348(16):1546-1554.
6. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.
7. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med*. 2006;34(1):15-21.
8. Williams MD, Braun LA, Cooper LM et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care*. 2004;8(5):R291-R298.
9. Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National Hospital Discharge Survey. *Chest*. 2003;124(3):1016-1020.
10. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med*. 1995; 333(13):845-851.
11. Taylor RW, Manganaro L, O'Brien J, et al. Impact of allogenic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. *Crit Care Med*. 2002;30(10):2249-2254.
12. Collignon PJ. Intravascular catheter associated sepsis: a common problem. The Australian Study on Intravascular Catheter Associated Sepsis. *Med J Aust*. 1994;161(6):374-378.
13. O'Brien JM Jr, Lu B, Ali NA, et al. Alcohol dependence is independently associated with sepsis, septic shock, and hospital mortality among adult intensive care unit patients. *Crit Care Med*. 2007;35:345-350.
14. Alberti C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med*. 2002;28(2):108-121.
15. Russell JA. Management of sepsis. *N Engl J Med*. 2006;355(16):1699-1713.
16. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med*. 2003;348(2):138-150.
17. Cohen J. The immunopathogenesis of sepsis. *Nature*. 2002;420(6917): 885-891.
18. Opal SM, Huber CE. Bench-to-bedside review: Toll-like receptors and their role in septic shock. *Crit Care*. 2002;6(2):125-136.
19. Morris GE, Parker LC, Ward JR, et al. Cooperative molecular and cellular networks regulate Toll-like receptor-dependent inflammatory responses. *FASEB J*. 2006;20(12):2153-2155.
20. Aderem A, Ulevitch RJ. Toll-like receptors in the induction of the innate immune response. *Nature*. 2000;406(6797):782-787.
21. Doyle SL, O'Neill LA. Toll-like receptors: from the discovery of NFkappaB to new insights into transcriptional regulations in innate immunity. *Biochem Pharmacol*. 2006;72(9):1102-1113.
22. Arcaroli J, Silva E, Maloney JP, et al. Variant IRAK-1 haplotype is associated with increased nuclear factor-kappaB activation and worse outcomes in sepsis. *Am J Respir Crit Care Med*. 2006;173(12):1335-1341.
23. Asehnoune K, Strassheim D, Mitra S, et al. Involvement of reactive oxygen species in Toll-like receptor 4-dependent activation of NF-kappa B. *J Immunol*. 2004;172(4):2522-2529.
24. Kwak SH, Mitra S, Bdeir K, et al. The kringle domain of urokinase-type plasminogen activator potentiates LPS-induced neutrophil activation through interaction with {alpha}V{beta}3 integrins. *J Leukoc Biol*. 2005;78(4):937-945.
25. Noubir S, Hmama Z, Reiner NE. Dual receptors and distinct pathways mediate interleukin-1 receptor-associated kinase degradation in response to lipopolysaccharide. Involvement of CD14/TLR4, CR3, and phosphatidylinositol 3-kinase. *J Biol Chem*. 2004;279(24):25189-25195.
26. Choudhry MA, Ahmad S, Ahmed Z, Sayeed MM. Prostaglandin E2 down-regulation of T cell IL-2 production is independent of IL-10 during gram-negative sepsis. *Immunol Lett*. 1999;67(2):125-130.
27. Taylor FB, Chang AC, Peer G, et al. Active site inhibited factor VIIa (DEGR VIIa) attenuates the coagulant and interleukin-6 and -8, but not tumor necrosis factor, responses of the baboon to LD100 Escherichia coli. *Blood*. 1998;91(5):1609-1615.
28. Brown KA, Brain SD, Pearson JD, et al. Neutrophils in development of multiple organ failure in sepsis. *Lancet*. 2006;368(9530):157-169.
29. van Griensven M, Probst C, Muller K, et al. Leukocyte-endothelial interactions via ICAM-1 are detrimental in polymicrobial sepsis. *Shock*. 2006;25(3):254-259.
30. Guo RF, Huber-Lang M, Wang X, et al. Protective effects of anti-C5a in sepsis-induced thymocyte apoptosis. *J Clin Invest*. 2000;106(10): 1271-1280.
31. Landry DW, Oliver JA. The pathogenesis of vasodilatory shock. *N Engl J Med*. 2001;345(8):588-595.
32. Thiemermann C, Szabo C, Mitchell JA, Vane JR. Vascular hyporeactivity to vasoconstrictor agents and hemodynamic decompensation in hemorrhagic shock is mediated by nitric oxide. *Proc Natl Acad Sci U S A*. 1993;90(1):267-271.
33. van der PT, de Waal MR, Coyle SM, Lowry SF. Antiinflammatory cytokine responses during clinical sepsis and experimental endotoxemia: sequential measurements of plasma soluble interleukin (IL)-1 receptor type II, IL-10, and IL-13. *J Infect Dis*. 1997;175(1):118-122.
34. Wang H, Bloom O, Zhang M, et al. HMG-1 as a late mediator of endotoxin lethality in mice. *Science*. 1999;285(5425):248-251.
35. Czermak BJ, Sarma V, Pierson CL, et al. Protective effects of C5a blockade in sepsis. *Nat Med*. 1999;5(7):788-792.
36. de Jonge E, Dekkers PE, Creasey AA, et al. Tissue factor pathway inhibitor dose-dependently inhibits coagulation activation without influencing the fibrinolytic and cytokine response during human endotoxemia. *Blood*. 2000;95(4):1124-1129.
37. Lawson CA, Yan SD, Yan SF, et al. Monocytes and tissue factor promote thrombosis in a murine model of oxygen deprivation. *J Clin Invest*. 1997;99(7):1729-1738.
38. Hou B, Eren M, Painter CA, et al. Tumor necrosis factor alpha activates the human plasminogen activator inhibitor-1 gene through a distal nuclear factor kappaB site. *J Biol Chem*. 2004;279(18):18127-18136.
39. Maris NA, de Vos AF, Bresser P, et al. Activation of coagulation and inhibition of fibrinolysis in the lung after inhalation of lipopolysaccharide by healthy volunteers. *Thromb Haemost*. 2005;93(6):1036-1040.
40. O'Brien JMJr, Abraham E. Human models of endotoxemia and recombinant human activated protein C. *Crit Care Med.* 2004;32(5 Suppl):S202-S208.
41. De Backer D, Verdant C, Chierego M, et al. Effects of drotrecogin alfa activated on microcirculatory alterations in patients with severe sepsis. *Crit Care Med*. 2006;34(7):1918-1924.
42. De Backer D, Creteur J, Dubois MJ, et al. The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. *Crit Care Med*. 2006;34(2):403-408.
43. Robbie LA, Dummer S, Booth NA, et al. Plasminogen activator inhibitor 2 and urokinase-type plasminogen activator in plasma and leucocytes in patients with severe sepsis. *Br J Haematol*. 2000;109(2): 342-348.
44. Zeerleder S, Schroeder V, Hack CE, et al. TAFI and PAI-1 levels in human sepsis. *Thromb Res*. 2006;118(2):205-212.
45. Jia L, Takahashi M, Morimoto H, et al. Changes in cardiac lipid metabolism during sepsis: the essential role of very low-density lipoprotein receptors. *Cardiovasc Res*. 2006;69(2):545-555.
46. Wendel M, Paul R, Heller AR. Lipoproteins in inflammation and sepsis. II. Clinical aspects. *Intensive Care Med*. 2007;33(1):25-35.
47. Rusavy Z, Sramek V, Lacigova S, et al. Influence of insulin on glucose metabolism and energy expenditure in septic patients. *Crit Care*. 2004;8(4):R213-R220.
48. Thissen JP, Underwood LE, Ketelslegers JM. Regulation of insulin-like growth factor-I in starvation and injury. *Nutr Rev*. 1999;57(6): 167-176.

49. Rivers E. The outcome of patients presenting to the emergency department with severe sepsis or septic shock. *Crit Care*. 2006;10(4): 154.
50. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet*. 2002;360(9328):219-223.
51. Levy RJ, Piel DA, Acton PD, et al. Evidence of myocardial hibernation in the septic heart. *Crit Care Med*. 2005;33(12):2752-2756.
52. Ertel W, Kremer JP, Kenney J, et al. Downregulation of proinflammatory cytokine release in whole blood from septic patients. *Blood*. 1995;85(5):1341-1347.
53. Hotchkiss RS, Nicholson DW. Apoptosis and caspases regulate death and inflammation in sepsis. *Nat Rev Immunol*. 2006;6(11):813-822.
54. Husain KD, Stromberg PE, Woolsey CA, et al. Mechanisms of decreased intestinal epithelial proliferation and increased apoptosis in murine acute lung injury. *Crit Care Med*. 2005;33(10):2350-2357.
55. Hotchkiss RS, Tinsley KW, Swanson PE, et al. Prevention of lymphocyte cell death in sepsis improves survival in mice. *Proc Natl Acad Sci U S A*. 1999;96(25):14541-14546.
56. Coopersmith CM, Stromberg PE, Dunne WM, et al. Inhibition of intestinal epithelial apoptosis and survival in a murine model of pneumonia-induced sepsis. *JAMA*. 2002;287(13):1716-1721.
57. Rudkowski JC, Barreiro E, Harfouche R, et al. Roles of iNOS and nNOS in sepsis-induced pulmonary apoptosis. *Am J Physiol Lung Cell Mol Physiol*. 2004;286(4):L793-L800.
58. Kortgen A, Niederprum P, Bauer M. Implementation of an evidence-based "standard operating procedure" and outcome in septic shock. *Crit Care Med*. 2006;34(4):943-949.
59. Shapiro NI, Howell MD, Talmor D, et al. Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. *Crit Care Med*. 2006;34(4):1025-1032.
60. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-1596.
61. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001; 345(19):1368-1377.
62. Trzeciak S, Dellinger RP, Abate NL, et al. Translating research to clinical practice: a 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. *Chest*. 2006;129(2):225-232.
63. Gao F, Melody T, Daniels DF, et al. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study. *Crit Care*. 2005; 9(6):R764-R770.
64. Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA*. 2001;286(6):700-707.
65. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247-2256.
66. Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA*. 1994;272(17):1354-1357.
67. Martin C, Viviand X, Leone M, Thirion X. Effect of norepinephrine on the outcome of septic shock. *Crit Care Med*. 2000;28(8):2758-2765.
68. Annane D, Sebille V, Troche G, et al. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA*. 2000;283(8):1038-1045.
69. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288(7):862-871.
70. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344(10):699-709.
71. Abraham E, Laterre PF, Garg R, et al. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med*. 2005;353(13):1332-1341.
72. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342(18):1301-1308.
73. Gajic O, Dara SI, Mendez JL, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med*. 2004;32(9):1817-1824.
74. Wheeler AP, Bernard GR, Thompson BT, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med*. 2006;354(21):2213-2224.
75. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-2575.
76. Van den BG, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345(19):1359-1367.
77. Van den BG, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006;354(5):449-461.
78. Raghavan M, Marik PE. Anemia, allogenic blood transfusion, and immunomodulation in the critically ill. *Chest*. 2005;127(1):295-307.
79. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409-417.
80. Drakulovic MB, Torres A, Bauer TT, et al. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet*. 1999;354(9193):1851-1858.
81. Tryba M, Cook D. Current guidelines on stress ulcer prophylaxis. *Drugs*. 1997;54(4):581-596.
82. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 Suppl):338S-400S.
83. Albert RK, Condie F. Hand-washing patterns in medical intensive-care units. *N Engl J Med*. 1981;304(24):1465-1466.
84. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471-1477.
85. Ely EW. The utility of weaning protocols to expedite liberation from mechanical ventilation. *Respir Care Clin N Am*. 2000;6(2):303-19,vi.
86. Rumbak MJ, Newton M, Truncale T, et al. A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. *Crit Care Med*. 2004;32(8):1689-1694.
87. Quartin AA, Schein RM, Kett DH, Peduzzi PN. Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. *JAMA*. 1997;277(13): 1058-1063.
88. Angus DC, Carlet J. Surviving intensive care: a report from the 2002 Brussels Roundtable. *Intensive Care Med*. 2003;29(3):368-377.
89. Jones C, Skirrow P, Griffiths RD, et al. Rehabilitation after critical illness: a randomized, controlled trial. *Crit Care Med*. 2003;31(10): 2456-2461.
90. Jones C, Griffiths RD, Skirrow P, Humphris G. Smoking cessation through comprehensive critical care. *Intensive Care Med*. 2001;27(9): 1547-1549.
91. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med*. 2006;354(2):166-178.
92. Potti A, Mukherjee S, Petersen R, et al. A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. *N Engl J Med*. 2006;355(6):570-580.
93. Chen HY, Yu SL, Chen CH, et al. A five-gene signature and clinical outcome in non-small-cell lung cancer. *N Engl J Med*. 2007;356(1): 11-20.
94. Holmes CL, Russell JA, Walley KR. Genetic polymorphisms in sepsis and septic shock: role in prognosis and potential for therapy. *Chest*. 2003;124(3):1103-1115.