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Mitchell M. Levy

Defining Sepsis **585**

Jean-Louis Vincent and Hakan Atalan Korkut

Definitions have been considered important in all fields of medicine, both at a patient level to facilitate accurate diagnosis and treatment, and at a research level to clarify patient inclusion criteria and interpretation of study results. Although there is agreement that sepsis refers to the host response to infection, the complexity of this response and of the patient groups affected, however, has meant that establishing accepted definitions of sepsis has been difficult. Recent consensus has provided global definitions of sepsis and infection, but further work is necessary to provide a means of more completely characterizing the sepsis response in individual patients, such that new interventions can be targeted better as physicians strive to decrease the still high mortality rates associated with this condition.

Biomarkers: Diagnosis and Risk Assessment in Sepsis **591**

Corey E. Ventetuolo and Mitchell M. Levy

Prompt diagnosis, intervention, and risk assessment are critical in caring for septic patient but remain difficult with currently available methods. Biomarkers may become useful adjuncts to clinicians and ultimately serve as targets for future therapeutic trials in sepsis. The most relevant markers are reviewed in this article, including interleukin-6, C-reactive protein, procalcitonin, triggering receptor expressed on myeloid cells-1, and biomarker panels.

The Immune System in Critical Illness **605**

John C. Marshall, Emmanuel Charbonney, and Patricia Duque Gonzalez

The mammalian immune system comprises a complex network of physical and molecular elements that protect the individual from danger in the environment. An evolutionarily ancient innate immune system recognizes danger through pattern-recognition receptors that are encoded in the genome and mobilizes a rapid and potent but nonspecific response. This response is responsible for the clinical syndromes of sepsis and the multiple organ dysfunction syndrome. The adaptive immune system is highly selective in its targets and is endowed with memory but is slow in initial activation. Critical illness results in derangements of all components of the immune response, but the very complexity of the process has frustrated attempts to correct these derangements and to affect significantly the clinical course of sepsis.

The Compensatory Anti-inflammatory Response Syndrome (CARS) in Critically Ill Patients 617

Nicholas S. Ward, Brian Casserly, and Alfred Ayala

Like the systemic inflammatory response syndrome (SIRS), the compensatory anti-inflammatory response syndrome (CARS) is a complex pattern of immunologic responses to severe infection or injury. The difference is that while SIRS is a proinflammatory response tasked with killing infectious organisms through activation of the immune system, CARS is a global deactivation of the immune system tasked with restoring homeostasis. Much research now suggests that the timing and relative magnitude of this response have a profound impact on patient outcomes.

The Coagulant Response in Sepsis 627

Marcel Levi

Sepsis is often associated with systemic intravascular activation of coagulation, potentially leading to widespread microvascular deposits of fibrin, and thereby contributing to multiple organ dysfunction. A complex interaction exists between activation of inflammatory systems and the initiating and regulating pathways of coagulation. A diagnosis of sepsis-associated disseminated intravascular coagulation can be made by a combination of routinely available laboratory tests, for which simple diagnostic algorithms have become available. Strategies to inhibit coagulation activation may theoretically be justified and are being evaluated in clinical studies.

The Heterogeneity of the Microcirculation in Critical Illness 643

Eva Klijin, C.A. Den Uil, Jan Bakker, and Can Ince

Microcirculation, a complex and specialized facet of organ architecture, has characteristics that vary according to the function of the tissue it supplies. Bedside technology that can directly observe microcirculation in patients, such as orthogonal polarization spectral imaging and sidestream dark field imaging, has opened the way to investigating this network and its components, especially in critical illness and surgery. These investigations have underscored the central role of microcirculation in perioperative disease states. They have also highlighted variations in the nature of microcirculation, both among organ systems and within specific organs. Supported by experimental studies, current investigations are better defining the nature of microcirculatory alterations in critical illness and how these alterations respond to therapy. This review focuses on studies conducted to date on the microcirculatory beds of critically ill patients. The functional anatomy of microcirculation networks and the role of these networks in the pathogenesis of critical illness are discussed. The morphology of microvascular beds that have been visualized during surgery and intensive care at the bedside are also described, including those of the brain, sublingual region, skin, intestine, and eyes.

Cellular Dysfunction in Sepsis 655

Mervyn Singer

Cellular dysfunction is a commonplace sequelum of sepsis and other systemic inflammatory conditions. Impaired energy production (related to mitochondrial inhibition, damage, and reduced protein turnover) appears to be a core mechanism underlying the development of organ dysfunction. The reduction in energy availability

appears to trigger a metabolic shutdown that impairs normal functioning of the cell. This may well represent an adaptive mechanism analogous to hibernation that prevents a massive degree of cell death and thus enables eventual recovery in survivors.

The Right Ventricle in Sepsis

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Chee M. Chan and James R. Klingler

Right ventricular dysfunction is common in sepsis and septic shock because of decreased myocardial contractility and elevated pulmonary vascular resistance despite a concomitant decrease in systemic vascular resistance. The mainstay of treatment for acute right heart failure includes treating the underlying cause of sepsis and reversing circulatory shock to maintain tissue perfusion and oxygen delivery. Decreasing pulmonary vascular resistance with selective pulmonary vasodilators is a reasonable approach to improving cardiac output in septic patients with right ventricular dysfunction. Treatment for right ventricular dysfunction in the setting of sepsis should concentrate on fluid repletion, monitoring for signs of RV overload, and correction of reversible causes of elevated pulmonary vascular resistance, such as hypoxia, acidosis, and lung hyperinflation.

Antimicrobial Management of Sepsis and Septic Shock

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Sat Sharma and Anand Kumar

Every patient who has sepsis and septic shock must be evaluated appropriately at presentation before the initiation of antibiotic therapy. However, in most situations, an abridged initial assessment focusing on critical diagnostic and management planning elements is sufficient. Intravenous antibiotics should be administered as early as possible, and always within the first hour of recognizing severe sepsis and septic shock. Broad-spectrum antibiotics must be selected with one or more agents active against likely bacterial or fungal pathogens and with good penetration into the presumed source. Antimicrobial therapy should be reevaluated daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs. Consider combination therapy in septic shock *Pseudomonas* infections in neutropenic patients. Combination therapy should be continued for no more than 3 to 5 days and de-escalation should occur following availability of susceptibilities. The duration of antibiotic therapy typically is limited to 7 to 10 days. Longer duration is considered if response is slow, if there is inadequate surgical source control, or if immunologic deficiencies are evident. Antimicrobial therapy should be stopped if infection is not considered the etiologic factor for a shock state.

Management of Sepsis: Early Resuscitation

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Emanuel P. Rivers, Victor Coba, Alvaro Visbal, Melissa Whitmill, and David Amponsah

Key links in the chain of survival for the management of severe sepsis and septic shock are early identification and comprehensive resuscitation of high-risk patients. Multiple studies have shown that the first 6 hours of early sepsis management are especially important from a diagnostic, pathogenic, and therapeutic perspective, and that steps taken during this period can have a significant impact on outcome. The recognition of this critical time period and the robust outcome benefit realized in previous studies provides the rationale for adopting early resuscitation as a distinct

intervention. Sepsis joins trauma, stroke, and acute myocardial infarction in having “golden hours,” representing a critical opportunity early on in the course of disease for actions that offer the most benefit.

Corticosteroids and Human Recombinant Activated Protein C for Septic Shock

705

Gwenhaël Colin and Djillali Annane

This article summarizes the current knowledge on the benefit/risk profile from the use of low-dose corticosteroids and activated protein C in treating septic shock. Physicians should consider using low-dose corticosteroids and drotrecogin alpha activated in the treatment of patients who have vasopressor-dependent septic shock with persistent signs of hypoperfusion, organ dysfunction, or hypotension. The optimal timing for initiating these treatments is from 6 to 24 hours from onset of shock. When patients are receiving these drugs, physicians should systematically screen for superinfection and serious bleeding events.

Glucose Control in Sepsis

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B. Taylor Thompson

Hyperglycemia is common during the course of critical illness and is associated with adverse clinical outcomes. Randomized controlled trials and large observational trials of insulin therapy titrated to achieve glucose values approximating the normal range (80 to 110 mg/dL) demonstrate improved morbidity and mortality in heterogeneous populations and have led to recommendations for improved glucose control. Patients who have septic shock, however, appear to be at higher risk for hypoglycemia, and a recent randomized trial focusing exclusively on patients who had severe sepsis did not show benefit. The recent Surviving Sepsis consensus statement recommends insulin therapy using validated protocols to lower glucose (less than 150 mg/dL) pending the results of adequately powered trials to determine if normalization (less than 110 mg/dL) of glucose is needed to optimize outcomes in patients who have severe sepsis.

Reducing Mortality in Severe Sepsis: The Surviving Sepsis Campaign

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Sean R. Townsend, Christa Schorr, Mitchell M. Levy, and R. Phillip Dellinger

This article traces the history and evolution of the Surviving Sepsis Campaign as a public health initiative through its several stages of development. The literature that has characterized clinical experiences with interventions related to the campaign is reviewed and conclusions discussed.

Sepsis Strategies in Development

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Steven P. LaRosa and Steven M. Opal

Severe sepsis, defined as inflammation and organ failure due to infection, continues to result in a mortality of approximately 30% despite advances in critical care. Current therapy includes timely administration of antibiotics, source control of infection, aggressive fluid resuscitation, support of failing organs, and use of activated protein C where clinically indicated. Bacterial mediators, including endotoxin and

superantigens, as well endogenous proinflammatory cytokines are considered important to the pathogenesis of sepsis-induced organ failure and are being targeted with numerous molecules and removal devices. Additional therapeutic strategies are aimed at restoring the natural anticoagulant levels, blocking deleterious effects of the complement cascade, reversing cytopathic hypoxia, and inhibiting excessive lymphocyte apoptosis. Molecules with pluripotent activity, such as interalpha inhibitor proteins and estrogen-receptor ligands, are also being investigated.