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Preface

R. Phillip Dellinger xiii

The Evolution of the Understanding of Sepsis, Infection, and the Host Response: A Brief History 637

Steven M. Opal

An appreciation for the problem of sepsis starts at the very beginning of recorded time. Early writings from the Middle East, China, and Greece indicate that waves of epidemics and sudden death in previously healthy people were noted as having special significance long before the germ theory of disease was first postulated. This article focuses on the evolution of understanding about the fundamental nature of infection and the host response that leads to sepsis.

Evolving Concepts in Sepsis Definitions 665

Jean-Louis Vincent, Eva Ocampos Martinez, and Eliezer Silva

Standardization of definitions has been considered important in sepsis to facilitate accurate diagnosis and treatment, to clarify patient inclusion criteria for clinical trials, and to enable comparison of results from different studies. However, despite development and publication of consensus conference definitions, diagnosis of sepsis remains difficult in clinical practice and many patients do not receive the early specific therapy that could benefit them. Concepts of sepsis need to evolve such that good global definitions are accompanied by better strategies for individual diagnosis and disease characterization; patients can then be treated rapidly and appropriately to maximize their chances of survival.

The Pathophysiology of Septic Shock 677

O. Okorie Nduka and Joseph E. Parrillo

There is a profound cellular dysfunction in sepsis, that clinically manifests as a continuum from simple, uncomplicated sepsis to severe sepsis, and finally to septic shock. Septic shock remains a significant challenge for clinicians. Recent advances in cellular and molecular biology have significantly improved our understanding of its pathogenetic mechanisms. These improvements will translate to better care and improved outcomes for these patients.

Animal Models of Sepsis 703

Sergio L. Zanotti-Cavazzoni and Roy D. Goldfarb

In this review, we start with a general discussion of relevant factors that can determine the validity of a sepsis animal model. We briefly review some of the currently used animal models of sepsis (small animal models

and large animal models). We discuss the clinical relevance of animal models in sepsis research today and address potential reasons for the apparent underperformance of animal models in predicting therapeutic success of novel drugs in clinical trials.

Microcirculatory Dysfunction in Sepsis

721

David J. Lundy and Stephen Trzeciak

This article discusses the role of microcirculatory dysfunction in the pathophysiology of sepsis, reviewing the role of the endothelium in modulating microcirculatory flow, discussing the function of nitric oxide in mediating microcirculatory blood flow, and outlining means of evaluating microcirculatory function in septic patients. Finally, potential novel therapies and challenges in treating microcirculatory dysfunction in septic patients are discussed.

Optimizing Antimicrobial Therapy in Sepsis and Septic Shock

733

Anand Kumar

This article reviews principles in the rational use of antibiotics in sepsis and septic shock and presents evidence-based recommendations for optimal antibiotic therapy. Every patient with sepsis and septic shock must be evaluated 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 *Pseudomonas* infections, and combination empiric therapy in neutropenic patients. Combination therapy should be continued for no more than 3 to 5 days and deescalation 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 in the case of immunologic deficiencies. Antimicrobial therapy should be stopped if infection is not considered the etiologic factor for a shock state.

Principles of Source Control in the Management of Sepsis

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John C. Marshall and Abdullah al Naqbi

The term “source control” encompasses all those physical measures used to control a focus of invasive infection and to restore the optimal function of the affected area. Source-control measures can be categorized into 3 broad modalities: drainage controls the liquid component of an infection by converting a closed space infection to a controlled sinus or fistula;

debridement is the physical removal of solid necrotic tissue (removal of an infected device can be considered a form of debridement); definitive measures seek to restore optimal function to the involved area. This article discusses specific approaches to source control in the abdomen, chest, and skin and soft tissues.

Sepsis-Induced Tissue Hypoperfusion

769

Alan E. Jones and Michael A. Puskarich

Sepsis affects the cardiovascular system through multiple mechanisms, and often these derangements result in tissue hypoperfusion. Tissue hypoperfusion is often present in the setting of overt shock, but it can also be present in patients without obvious shock physiology. If left untreated, tissue hypoperfusion contributes to the development of multiple organ dysfunction and, ultimately, death. Therefore, it is critical for the clinician to understand the pathophysiology, recognition, and treatment of sepsis-induced hypoperfusion.

Inotrope and Vasopressor Therapy of Septic Shock

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Steven M. Hollenberg

When fluid administration fails to restore an adequate arterial pressure and organ perfusion in patients with septic shock, therapy with vasoactive agents should be initiated. The ultimate goals of such therapy in shock are to restore effective tissue perfusion and to normalize cellular metabolism. The efficacy of hemodynamic therapy in sepsis should be assessed by monitoring a combination of clinical and hemodynamic parameters. Although specific end points for therapy are debatable, and therapies will inevitably evolve as new information becomes available, the idea that clinicians should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis remains a fundamental principle.

Hemodynamic Monitoring in Sepsis

803

Brian Casserly, Richard Read, and Mitchell M. Levy

Tissue hypoperfusion is an important factor in the development of multiple organ failure. Therefore, recognition of sepsis-induced tissue hypoperfusion and timely clinical intervention to prevent and correct this are fundamental aspects of managing patients with sepsis and septic shock. Hemodynamic monitoring plays a key role in the management of the critically ill and is used to identify hemodynamic instability and its cause and to monitor response to therapy. However, the utility of many forms of hemodynamic monitoring that are used in management of sepsis and septic shock remain controversial and unproven. This article examines emerging technologies as well as more established techniques used to monitor hemodynamics in sepsis and assesses their potential roles in optimization of sepsis-induced tissue hypoperfusion.

Steroid Therapy of Septic Shock

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Charles L. Sprung, Serge Goodman, and Yoram G. Weiss

Despite their potential benefits, corticosteroids have adverse effects and the benefits and risks must be balanced in determining whether they should be used or not. Some of the serious adverse effects noted in patients with critically illness have included superinfections and critical illness polyneuromyopathy. This article reviews the subject of steroid treatment of patients with septic shock and weighs the advantages and disadvantages of steroid treatment. It reviews and contrasts several low- and high-dose steroid studies, and makes recommendations for future practice.

Genetic Polymorphisms in Sepsis

835

Allen Namath and Andrew J. Patterson

This article is meant to serve as a summary of scientific advances from the past 5 years with regard to genetic polymorphisms in sepsis. It is also meant to highlight some of the discoveries that may improve our ability to identify vulnerable patients at earlier time points in sepsis, when interventions are more likely to have a positive effect. The article begins with an overview of polymorphism studies and a discussion of candidate gene versus genome-wide association studies. Next, an overview of polymorphisms associated with sepsis is presented. The overview includes detailed descriptions of E-selectin, apolipoprotein E, and C-reactive protein polymorphisms and a table in which numerous other sepsis-related polymorphisms are introduced. An examination of consortia-based projects that have the potential to catalyze sepsis research is included as is a preview of technological advancements that are likely to strongly influence sepsis studies in the near future. The article concludes with a brief consideration of ethical and social issues relevant to human genomic studies.

Performance Improvement in the Management of Sepsis

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Christa Schorr

Performance improvement in medicine based on evidence-based guidelines is a persistent challenge for clinicians. Challenges include deficiencies in collaboration, resistance to change, complex algorithms, inadequate resources, and inability to collect data and provide feedback. In severe sepsis this is further compounded by the perceived importance of early intervention and considerable conflicting literature. The bundle concept first adopted for mechanically ventilated patients and then for central line insertion, has now been applied to care for the patient with severe sepsis. The bundle concept in severe sepsis facilitates the provision of best practice consistent care to eligible patients with a structure to measure compliance. Time sensitive bundle indicators allow for uniform data collection and reporting. Successful modification of clinical practice may require months or years. The success of the program relies upon the cross-departmental collaboration and support generated before implementation and the ability to deliver timely feedback to facilitate change in performance.

Multicenter Clinical Trials in Sepsis: Understanding the Big Picture and Building a Successful Operation at Your Hospital **869**

R. Phillip Dellinger, Christa Schorr, and Stephen Trzeciak

The environment for clinical trials in sepsis has long been identified as challenging and full of road blocks and land mines. Unlike many other diagnoses (ie, cancer, acute myocardial infarction) relevance of animal studies and predictive capability of phase II trials for dose generation is less clear. The members of the investigative team must realize the essentials for success in a multicenter clinical trial. It is also useful and important to understand the big picture of clinical trial development as well as properly functioning interfaces among sponsor, contract research organizations, and investigative sites. Because early enrollment into sepsis clinical trials is usually required, collaboration between emergency medicine and critical care is needed.

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