CHAPTER 27

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Sepsis

CHAPTER OUTLINE

LEARNING OBJECTIVES

After reading this chapter, one should be able to:

- Discuss the epidemiology (including risk factors) of sepsis in the pediatric population.
- Discuss the inflammatory cascade triggered by bacterial organisms.
- Discuss the cellular responses to systemic infection including the roles of:
  - Inflammatory cells
  - Endothelial cells
  - Cytokines and other mediators
  - Coagulation system
- Understand the clinical signs and symptoms that result from generalized and organ specific inflammation and injury.
- Understand the role of appropriate empiric antibiotic coverage, adequate fluid resuscitation and pharmacologic hemodynamic support.
- Discuss the treatment of sepsis, focusing on the underlying rationale for therapies including:
  - Antibiotics
  - Inotropic support
  - Vasoactive agents
  - Corticosteroids
  - Monoclonal antibodies
  - Cytokine inhibitors and analogues
  - Agents targeted to the coagulation system
- Appreciate the role of genetic regulation of this myriad of immunologic and physiologic responses and speculate on the future directions of basic and applied clinical science research

INTRODUCTION

The health care provider faced with the management of a child with septic shock relies on a comprehensive understanding of the numerous disciplines embodied in the practice of pediatric critical care medicine. The child with septic shock may have simultaneous derangements in the function of virtually every system of the body including: cardiovascular, respiratory, immune, renal, coagulation, hepatic, metabolic and neurologic. The degree to which physiologic alterations are manifest in a given patient is variable and influenced by multiple host and non-host factors including: the developmental stage, the presence of comorbidities, pathogen-related factors, and genetic influences on both the host inflammatory

response as well as the response to pharmacologic agents, all combining to have a profound influence on outcome. The clinician must possess a systematic and multifaceted approach to these critically ill patients. The goal of this chapter is to provide a comprehensive description of the epidemiology, biology and pathophysiology (at both the cellular and organ level) of sepsis, as well as outlining the current principles of managing septic shock. It will be apparent that optimal management requires a strong working knowledge of cardiovascular physiology, infectious diseases, multiple organ interactions, immunity, coagulation, pharmacology, and the molecular biology of inflammation.

DEFINITIONS

Before reviewing the epidemiology of pediatric sepsis, it must be appreciated that the conclusions of prevalence studies have been obscured in the past by several factors including a lack of a reliable case definition. It has only been in the 1990s that consensus definitions for sepsis and septic shock were achieved. It was hoped that the development of standard definitions would not only enable accurate characterization of the epidemiology of sepsis, but also serve to stratify patients early in the course of sepsis for the purpose of clinical studies aimed at testing novel therapies. The most widely used definition of pediatric sepsis/septic shock is based on the 1992 American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference, with adaptations for the pediatric population. The following four definitions resulted from these discussions: *SIRS*, *sepsis*, *septic shock*, and *severe sepsis*. Although there is overlap between some of these terms (particularly between septic shock and severe sepsis), each is intended to define a particular patient population.

Longstanding clinical observations have identified the presence of tachycardia, tachypnea, hyperthermia and leukocytosis as signs of infection, though these responses may also be present in the absence of any apparent infectious source. As a result, this physiologic response was defined as the systemic inflammatory response syndrome (SIRS). *SIRS* defines a state of inflammation/immune activation in a child and is based on the presence of at least two of the four criteria listed in Table 27-1. Thus, patients with diverse clinical conditions such as sepsis, pancreatitis, burns, or severe trauma can meet criteria for SIRS. It has been argued that the SIRS definition is non-specific and that too broad a range of patients are ultimately classified as having SIRS. Nevertheless, the criteria have been widely used in both prescriptive and interventional studies to enhance the "capture" of all patients at risk for the subsequent development of severe sepsis or septic shock.

SIRS is a state of inflammatory/ immune activation and is based on the presence of at least two of the four following clinical criteria: Temperature >38°C or <36°C, heart rate >90th percentile for age, respiratory rate >90th percentile for age, or hyperventilation to $PaCO_2$ <32 mm Hg. The definition attempts to "capture" all patients at risk for the subsequent development of severe sepsis or septic shock.

TABLE 27-1

CRITERIA FOR SIRS, SEVERE SEPSIS, AND SEPTIC SHOCK

Criteria for SIRS

Patients must present with at least 2 of the following 4 criteria:

1. Temperature >38°C or <36°C (as determined by central temperature)

2. Heart rate >90th percentile for age

3. Respiratory rate >90th percentile for age, or hyperventilation to $PaCO_2$ <32 mm Hg

4. White blood cell count >12,000 cells/μL, or <4,000 cells/μL

Criteria for severe sepsis

Sepsis plus any <u>one</u> of the following:

1. Glasgow coma score <15 in the absence of CNS disease

2. Arterial blood lactate >1.6 mmol/L, or venous blood lactate >2.2 mmol/L

3. Urine output <1 mL/kg/h for 2 consecutive hours with a urinary catheter in place

Criteria for septic shock:

Sepsis with hypotension (two distinct measurements of blood pressure <3rd percentile for age) after administration of 20 mL/kg of crystalloid or colloid, plus any <u>one</u> of the following:

1. Requirement for inotropic or vasopressor support (excluding dopamine ≤5 μg/kg/min)
2. Any of the diagnostic criteria for severe sepsis listed above

Sepsis is defined as a SIRS response which is secondary to an infection, either documented by microbiology cultures or other clinical evidence of infection. *Severe sepsis* is defined by sepsis criteria plus evidence of insufficient end organ perfusion (Table 27-1). Finally, *septic shock* is defined by sepsis criteria plus hypotension (two distinct measurements <3rd percentile for age) after the administration of at least 20 mL/kg of crystalloid or colloid, in addition to the criteria listed for severe sepsis (Table 27-1).

These criteria have been used extensively for conducting clinical investigations and have proven to be of value despite criticism for lack of both sensitivity and specificity. The latest consensus conference was convened in 2007 to further refine the diagnostic criteria and therapeutic recommendations, with specific considerations for the pediatric population. Published in 2008, the Surviving Sepsis Campaign aims to improve the outcome in sepsis worldwide. The refinement of pediatric-specific criteria for septic shock is also intended to aid future clinical trials and epidemiologic investigations in pediatric sepsis.

EPIDEMIOLOGY

The few published pediatric-specific studies illustrate the importance of sepsis in this age range. Proulx analyzed the incidence and outcome of SIRS, sepsis, severe sepsis, and septic shock in a single institution. Over 1,000 admissions were analyzed over a 1-year period. SIRS was present in 82% of patients, while 23% had sepsis, 4% had severe sepsis, and 2% had septic shock. The overall mortality for this population was 6% with a majority of deaths occurring in patients with multiple organ dysfunction syndrome (MODS).

An epidemiologic study using discharge International Classification of Disease, 9th revision (ICD-9) codes reviewed hospital records from seven large states representing nearly one-quarter of the United States population. While the criteria used for inpatient coding at discharge are not identical to ACCP/SCCM Consensus Conference criteria, the study estimated an incidence of 42,371 cases of severe sepsis in individuals less than 20 years of age (0.6 cases/1,000 population). The highest incidence was in neonates (5.2 cases/1,000 population), compared to children ages 5–14 who had an incidence of 0.2 cases/1,000 population. The overall mortality rate was 10.3% (4,364 deaths nationally) consistent with the frequent observation that the mortality rate remains lower than comparable adult data. The study estimated an annual national health care cost of $1.7 billion associated with severe sepsis in children. A follow-up study with the same methodology appeared to show a 13% increase in the absolute number of cases of severe sepsis from 1995 and 1999 with the majority of this increase accounted for by severe sepsis in children less than 1 year of age. The mortality rate had decreased to 9.0% during this time period.

Collectively, these data illustrate that sepsis is a major health problem on the basis of incidence, mortality, and health care costs. There remains a need for further, well-designed epidemiologic studies of pediatric sepsis. Future studies will enhance our understanding of not only epidemiology, but also the impact of new diagnostic and therapeutic approaches resulting from improved design of interventional trials specific to the pediatric population.

CLINICAL PRESENTATION

Common clinical manifestations of sepsis include: fever or hypothermia, tachypnea, tachycardia, leukocytosis or leukopenia, thrombocytopenia and change in mental status.

Sepsis is a systemic disease and can impact the functioning of all organ systems. The most common clinical manifestations of sepsis include: fever or hypothermia, tachypnea, tachycardia, leukocytosis or leukopenia, thrombocytopenia, and change in mental status. One of the earliest signs of infection is fever which results from the pyrogenic effect of cytokines, particularly interleukin (IL)-1β and tumor necrosis factor (TNF)-α. Presentation with hypothermia can also occur, but is more common in infants.

One traditional classification of shock states divides this clinical state into three broad categories: hypovolemic, cardiogenic and distributive shock. The shock associated with

sepsis is unique in that all three forms are likely to be present. Hypovolemic shock results from capillary leak, increased insensible losses, and decreased effective blood volume secondary to venodilation. Cardiogenic shock is related to direct myocardial depression, the cause(s) of which remains the focus of investigation. Finally, distributive shock is often apparent as brisk capillary refill, widened pulse pressure and bounding peripheral pulses and is caused by abnormally decreased systemic vascular resistance from pathologic vasodilation. The particular pattern of these hemodynamic physiologic perturbations manifested by any individual patient can be variable. Some children have increased cardiac output with diminished systemic vascular resistance characteristic of distributive shock or the so-called "warm" shock state. In stark contrast to adults, in which this hemodynamic profile (increased cardiac output/decreased systemic vascular resistance) is most common, children more frequently present with depressed cardiac output and elevated systemic vascular resistance. These patients appear cool with diminished pulses and poor capillary refill that is characteristic of the "cold" shock state. While important to recognize that patients may transition from one state to another, the presence of hypotension is often a late and particularly ominous sign that requires prompt intervention as its presence is associated with increased mortality.

> Children with sepsis may have hemodynamic characteristics that transcend traditional classification. They often have elements of hypovolemia, cardiac dysfunction and abnormal vascular tone.

Patients with sepsis often present with alterations in their respiratory system, notably tachypnea that reflects a compensatory respiratory alkalosis aimed at neutralizing a metabolic acidosis related to hypoperfusion and anaerobic metabolism. Chest x-ray findings can reveal a small heart in the presence of hypovolemia with few vascular markings. Alternatively, the combination of capillary leak, decreased myocardial function and the result of fluid resuscitation in some children with sepsis can result in pulmonary edema. Rapid progression to acute respiratory failure from ARDS is not uncommon. All organ systems and ultimately cellular functions are affected by poor perfusion and decreased oxygen delivery related to depressed cardiac and respiratory function. In addition, there may be direct injurious effects of bacterial toxins and circulating cytokines such as triggering of programmed cell death or apoptosis. The neurologic state of a child with sepsis is frequently altered and can range from agitation or irritability to frank obtundation. This depressed mental status can be present even in the absence of meningitis as a manifestation of cerebral hypoperfusion. Skin manifestations are not uncommon and can include petechiae and purpura that are ominous signs of disseminated intravascular coagulation (DIC) and purpura fulminans secondary to meningococcemia. Diffuse erythema secondary to toxic shock syndromes can be present. There is also an increasing appreciation of sepsis-induced microvascular angiopathy contributing to distal skin and organ ischemia. An initial thorough and detailed physical exam provides both important clues to the diagnostic possibilities of pediatric septic shock and the underlying hemodynamic profile. However, serial exams are imperative to follow pathophysiologic changes and to gauge the impact of therapeutic interventions in reversing the manifestations of shock.

> In the septic child, the combination of capillary leak, decreased myocardial function and the result of fluid resuscitation may result in rapid progression to acute respiratory failure.

PATHOGENESIS OF SEPSIS

Data from both clinical and basic science studies have supported the hypothesis that pathogens and/or their products initiate a host immune response that triggers widespread inflammation causing tissue injury and organ dysfunction. Potential initiating pathogens include Gram-negative and Gram-positive bacteria, viruses, fungi and protozoa. In some cases, overwhelming spread of pathogens (e.g. bacteremia) with release of toxins (e.g. endo- or exotoxins) may directly injure the host resulting in organ dysfunction.

Higher order organisms have evolved an immune system to eradicate pathogens which has evolved to include two systems: the innate or natural immune system and the acquired or adaptive immune system. The innate immune system is responsible for the highly conserved function of recognizing pathogens and mounting an effector response. It includes a series of molecules located on the cell surface termed pattern-recognition receptors (PRR) which are capable of recognizing a broad array of conserved structures on a variety of

The cells of the innate immune system contain cell surface molecules termed pattern-recognition receptors (PRR). These receptors are capable of recognizing a broad array of conserved structures on a variety of pathogens (so-called pathogen-associated molecular patterns, or PAMP's). Examples of PAMP's include: lipopolysaccharide, lipoteichoic acid, viral RNA and bacterial DNA.

Toll-like receptors (TLR) are pathogen recognition receptors that have a critical role in sepsis. TLR4 is active in recognition of LPS on Gram-negative bacteria whereas TLR2 is active in the recognition of lipotechoic acid on Gram-positive bacteria.

A hallmark of sepsis is an immune response that appears to become unregulated resulting in an overwhelming proinflammatory response and host auto-destruction. This characteristic systemic inflammatory response is seen frequently in response to infection, but can also be observed in association with non-infectious triggers (e.g. trauma, burns, pancreatitis, cardiopulmonary bypass).

pathogens (so-called pathogen-associated molecular patterns, or PAMP's). Examples of PAMP's include: lipopolysaccharide (LPS) on Gram-negative bacteria, lipoteichoic acid on Gram-positive bacteria, mannans on yeast, double-stranded RNA of RNA viruses and unmethylated, CpG DNA from bacteria. The effector responses that are regulated by the innate immune system (e.g. phagocytes, complement) are activated immediately upon infection and are designed to rapidly inhibit the replication of microorganisms.

These cell surface pattern-recognition receptors (PRR) are expressed on most antigen presenting cells of the innate immune system and represent diverse families of proteins. One group of PRRs, the Toll-Like Receptors (TLR), has been identified as perhaps the most critical pathogen recognition receptor family in the context of sepsis biology. Other families of PRR include the C-type collagenous lectins (collectins) that bind to a variety of carbohydrate moieties on cells, bacteria and viruses. Most members of this family share structural homology to the complement protein C1q and can functionally substitute for C1q in activating the complement cascade. Another family of PRR possesses leucine-rich regions critical for protein-protein interactions that are necessary for immune recognition. Examples of these leucine rich receptors include CD14, a receptor on the cell surface of macrophages that binds to LPS and the macrophage scavenger receptor that binds to bacterial cell walls. Unbound circulating PRRs exist and include pentraxins, such as C-reactive protein, an acute phase reactant synthesized by the liver and lipopolysaccharide-binding protein (LBP) which binds to LPS to optimize its binding to the CD14/Toll-like receptor cellular complex.

Another key component of innate immunity is the complement system. The complement system is a complex cascade of proteins that possesses a broad array of anti-pathogen activities including: opsonization (C3), neutrophil chemotaxis (C5a), perforating cytotoxicity (C6-9, MAC complex) and the ability to bind to and directly lyse viruses (C1). An in depth discussion of the role of complement in the response to infection is beyond the scope of this chapter, but has been recently summarized. In summary, the host possesses a ubiquitous and diverse set of pathogen recognition receptors which function to protect the host from infectious challenges, but at the expense of triggering powerful effector responses.

Paramount to effector responses of the innate immune system is a proinflammatory action of numerous cytokines and chemokines. These biologically active proteins are critical to the activation and recruitment of cellular components of the adaptive immune system. While necessary for pathogen clearance, this acute, proinflammatory immune response must also ultimately subside in order to reestablish homeostasis and avoid cellular and tissue damage. A key pathophysiologic feature of sepsis is that this immune response often appears to become unregulated resulting in an overwhelming proinflammatory response and host auto-destruction. This characteristic systemic inflammatory response seen frequently in response to infection can also be observed in association with non-infectious triggers (e.g. trauma, burns, pancreatitis, cardiopulmonary bypass).

Inflammatory Cascade of Sepsis

LPS Recognition: Recent epidemiologic surveys of the causative agents of sepsis have indicated an increase in the incidence of Gram-positive organisms such that there is a roughly equivalent prevalence between these and Gram-negative organisms. Historically, sepsis research has focused on the role of Gram-negative bacteria in evoking a pathologic response. The structure of endotoxin shows three domains: an outer polysaccharide hydrophilic chain which determines the O-antigenicity, an acidic core region, and a lipid-rich region. Gram-negative organisms possess endotoxins with variable repeats of mono- and heteropolysaccharides with complex side chain structure to provide a basis for distinct antigenicity. The O-region is linked via an acidic core to the lipid A region that is highly conserved and responsible for much of the toxicity attributed to intact LPS.

A series of seminal observations have determined the molecular mechanisms by which the classic PAMP, LPS, initiates a proinflammatory response. First, a strain of LPS-resistant mice, the C3H/HeJ strain, was identified and its resistance was found to be attributed to a single genetic mutation. Second, it was shown that the lethal effects of endotoxin could be conferred by transfer of hematopoietic cells. Endotoxin tolerant mice could be rendered

LPS-sensitive after reconstitution with hematopoietic cells derived from the monocyte/macrophage lineage from an LPS-sensitive strain. Third, stimulation of monocyte-derived cells with endotoxin resulted in production of several cytokines and chemokines critical to the systemic inflammatory response. Among these, TNF and IL-1 were shown to be critical initiators of the septic response and could in fact mimic the endotoxin response. Finally, the elucidation of the LPS receptor assisted the identification of those signal transduction pathways by which endotoxin triggers inflammatory gene expression.

LPS receptor: Membrane bound CD-14 was shown to be required for LPS signaling. However, it lacked a transmembrane extension required for cytoplasmic signaling indicating the presence of additional components of the receptor complex. Investigators working with *Drosophila* had identified a gene, Toll, which was responsible for dorsoventral polarization in embryonic development. When Toll was functionally mutated, it was demonstrated to play a key role in host defense against *Aspergillus fumigatus*. Homology between the Toll-like receptors and the mammalian IL-1 family of receptors was discovered and provided additional evidence that this family was crucial to the human innate immune response. Finally, it was determined that the C3H/HeJ mouse strain which is hyporesponsive to LPS possessed a mutation in Toll-like receptor 4 (TLR4), providing further evidence that this receptor was necessary for LPS signaling. TLR4 is one of ten mammalian Toll-like receptors that have been cloned to date, each being activated by a specific set of ligands. Since these discoveries, other members of the LPS-receptor complex have been elucidated and include both MD-2 and MyD88. It is also known that circulating LPS-binding protein (LBP) facilitates LPS binding to the cell surface receptor complex. Together these components are able to "sense" LPS at the cell surface and transmit this signal via a series of complex pathways. Similarly, the products of Gram-positive organisms, notably the cell wall component lipotechoic acid, activate cell activation through the related Toll-like receptor 2 (TLR2).

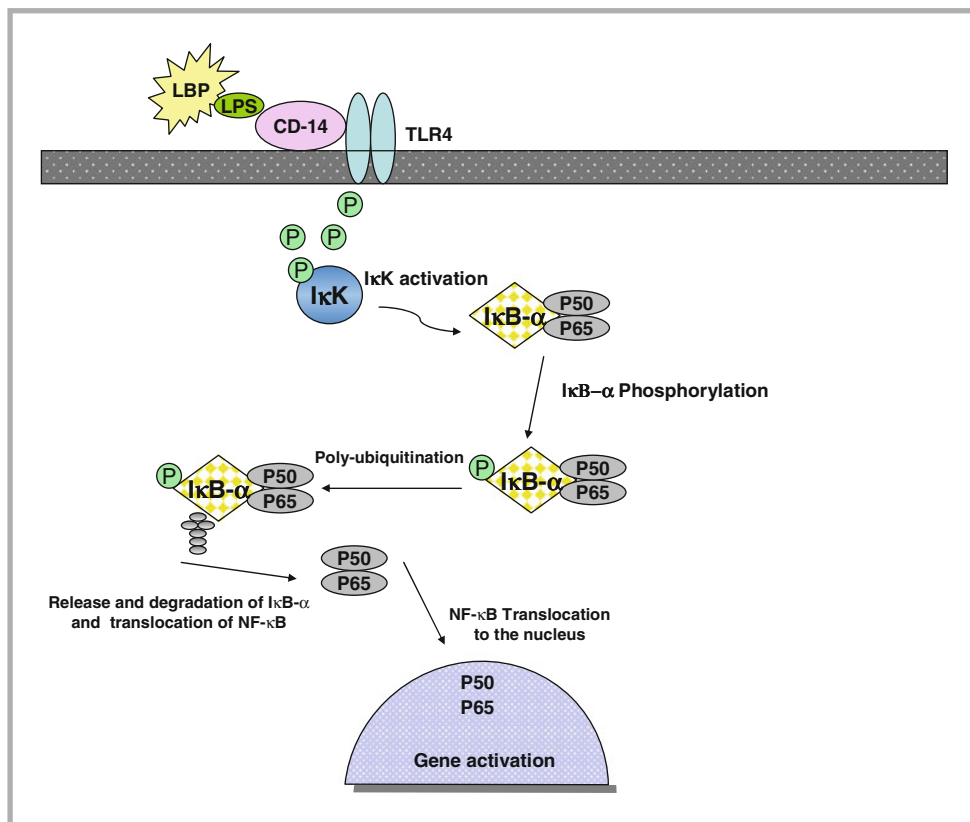# Signal Transduction Pathways

After engagement of cell surface receptors (e.g. TLR2 and TLR4), several important signal transduction pathways are activated that elicit a number of transcriptional factors responsible for inflammatory gene expression. Among these, the nuclear factor-κB (NF-κβ) and the mitogen activated protein kinase (MAPK) pathways play a prominent role in regulating the expression of a number of inflammatory gene products key to propagating the sepsis response. In the case of NF-κB, stimulation of the LPS receptor causes phosphorylation of the Inhibitor of κB Kinases (IκK) which in turn phosphorylates the intracellular inhibitor of NF-κB, I kappa B (IκB). Upon phosphorylation, IκB undergoes poly-ubiquination followed by proteosomal degradation. The removal of IκB effectively unmasks a nuclear translocation sequence on NF-κB enabling it to proceed into the nucleus to bind to NF-κB consensus sequences present on the promoter regions of many inflammatory genes: cytokines including TNF, chemokines including IL-8, adhesion molecules including E-selectin and others such as iNOS (see Fig. 27-1). The role of NF-κB in sepsis is supported by studies demonstrating that survivors and non-survivors of sepsis are distinguishable on the basis of NF-κB binding activity in peripheral blood mononuclear cells. In addition, in sepsis-induced ARDS, increased activation of NF-κB in macrophages obtained by BAL is found in ARDS patients when compared to ICU controls.

To a similar degree, the MAPK signaling pathways are important in mediating the septic response. Three MAPK pathways exist: p38 protein kinase, extracellular-regulated protein kinase (ERK), and c-Jun-terminal kinase (JNK). Evidence exists for the role of each of these signaling pathways in sepsis. TNF production by neutrophils and macrophages is dependent on p38 activation. LPS stimulation of monocytes activates JNK with downstream activation of activating protein-1 (AP-1) and subsequent IL-1β production. LPS induction of TNF is in part dependent on ERK pathway activation. Together, these two pathways, NF-κB and MAPK's, appear to be critical to the propagation of signals from the cell surface to the nucleus where expression of inflammatory gene products occurs. As such, these pathways remain valid targets for future strategies in modulating the septic response.

Nuclear factor-κB (NF-κβ) and the mitogen activated protein kinase (MAPK) pathways play a prominent role in regulating the expression of a number of inflammatory gene products key to propagating the sepsis response.

FIGURE 27-1

Pathway of LPS Activation of NF-kB Pathway. Pathway of LPS-induced activation of the NF-kB pathway resulting in inflammatory gene expression. *LPS* lipopolysaccharide, *LBP* LPS binding protein, *TLR4* Toll-like Receptor-4, *NF-kB* nuclear factor kappa-B (transcriptional activating heterodimeric complex), *IkB-a* inhibitor of kappa B-alpha, *IkK* I kappa B kinase complex and *P* denotes phosphorylation

TNF possesses numerous functions in inflammation such as inducing adhesion molecules and chemokines that facilitate leukocyte-endothelial cell adhesion and inducing nitric oxide synthase (iNOS) which mediates pathologic vasodilation. TNF also upregulates tissue factor and inhibits protein C to create a pathologic procoagulant state in the vasculature. Clinically, levels of TNF correlate with mortality, the development of shock and purpura fulminans and with the development of sepsis-induced ARDS and shock.

Principal Gene Products/Mediators of the Septic Response

While numerous proteins have been shown to play a role in the septic response, a full review of each protein's function is beyond the scope of this study guide. Instead, we aim to highlight some known principle mediators in this cascade.

Tumor Necrosis Factor-α

Evidence that TNF mediates the septic response stems from numerous observations: it is produced by hematopoietic cells, its expression is temporally related to the development of septic shock, recombinant TNF induces experimental septic shock in animals, and passive immunization against TNF attenuates endotoxin-mediated responses. TNF possesses numerous functions in inflammation such as driving adhesion molecule and chemokine expression to facilitate leukocyte-endothelial cell adhesion; upregulating tissue factor and inhibition of protein C to create a pathologic procoagulant state in the vasculature; and inducing nitric oxide synthase (iNOS) which mediates pathologic vasodilation. In human studies, levels of TNF have been shown to correlate with mortality, with the development of shock and purpura fulminans and with the development of sepsis-induced ARDS and shock.

Interleukin-1β

The name, IL-1, is now used to describe the family of proteins including two agonists (IL-1α and IL-1β) and one antagonist, the IL-1 receptor antagonist protein (IL-1Ra). IL-1β which is secreted, mediates much of the systemic effects attributed to IL-1 release in sepsis. Synthesized as a propeptide, IL-1β requires proteolytic cleavage by the IL-1 converting enzyme (ICE) to become bioactive. IL-1β utilizes the 80-kDa type I receptor which is

associated with a number of adapter proteins (e.g. MyD88,TNF receptor-associated factor 6 (TRAF6) and interleukin-1 receptor-associated kinase (IRAK)) to propagate signals through both the NF-κB and AP-1 pathways. IL-1β infusion elicits fever, hypotension and leukocytic infiltration to the lungs. In a manner similar to TNF, IL-1 stimulates monocyte activation and phagocytosis, increases adhesion molecule expression, and increases tissue factor expression while inhibiting thrombomodulin secretion, thus creating a procoagulant state. When detected in the circulation of septic patients, IL-1 levels also correlate with mortality. Of note, the IL-1Ra is a circulating inhibitor of IL-1β that binds to the IL-1 receptor without initiating a signal. The expression of IL-1Ra has been shown to follow peak expression of IL-1. It is speculated that IL-1Ra is an endogenous regulator of IL-1 effects. However, in clinical trials, IL-1Ra infusion failed to improve mortality in sepsis.

Adhesion Molecules

Furthering our molecular understanding of sepsis-induced organ dysfunction was the identification of the "leukocyte-endothelial cell adhesion cascade". This cascade is characterized by cytokine activation of the selectin family of adhesion molecules (e.g. E-selectin) on the endothelium which initiate a process of neutrophil "rolling" via interaction with sialyated moieties constitutively present on circulating neutrophils. Activation of the "rolling" neutrophil results in both increased expression and activation of the integrins which in turn bind to intercellular adhesion molecule (ICAM)-1 that is upregulated on the endothelial cell surface by TNF and IL-1β. This integrin-ICAM-1 interaction mediates firm adhesion of the neutrophil to the endothelial cell surface. Finally, in response to various chemotactic cytokines or chemokines, neutrophils migrate to the site of inflammation. Release of both oxygen- and nitrogen-based radical species and proteases by the neutrophils may ultimately contribute to cellular injury and organ dysfunction.

Nitric Oxide

Nitric oxide (NO) is responsible for endothelium-derived relaxation of blood vessels. Three isoforms of nitric oxide synthase are responsible for production of NO: type I, a neuronal isoform (nNOS); type II, an inducible isoform (iNOS) and type III, a constitutive, endothelial isoform (eNOS). TNF and IL-1β are capable of inducing iNOS and increased levels of circulating stable byproducts of NO are found in both septic adults and children who simultaneously display low systemic vascular tone. This supports the hypothesis that NO plays a principal role in septic shock via pathologic vasodilation. It has also been suggested that TNF and IL-1β may be the so-called "myocardial depressant factors" by increasing circulating NO through induction of iNOS ; however, it is not clear that NO is the exclusive mediator of these effects. In light of the evidence supporting the role of NO in septic shock, clinical trials employing NO synthesis inhibitors in septic shock were initiated. Though early clinical reports and small studies reported that NOS inhibitors could significantly improve blood pressure, this was at the expense of decreasing cardiac output secondary to increased afterload. As a not uncommon hemodynamic profile in pediatric septic shock is decreased cardiac output and elevated systemic vascular resistance, it is not cleat that NOS inhibitors will have a therapeutic role in pediatric (or adult) sepsis in the future.

Putative Role of "Late" Mediators in the Pathogenesis of Sepsis

Studies employing agents directed against the early mediators of the septic response have been mostly ineffectual. This has led to the hypothesis that additional molecules with delayed kinetics of expression may influence the outcome in sepsis. As an example, it was observed that LPS-challenged mice often die long after peak expressions of TNF and IL-1β suggesting that late-acting proteins may contribute to endotoxin-induced mortality. Investigators searching for late expressed proteins identified a member of the high mobility group (HMG)-1 non-histone chromosomal protein family in conditioned media 16 h after LPS-stimulation of macrophages. This protein renamed HMGB1 is a known ligand for the receptor for advanced

glycation end products (RAGE). The RAGE receptor is expressed on monocytes and vascular smooth muscle. Binding by HMGB1 activates both the NF-κB and MAPK pathways. Increased expression of HMGB1 was found in endotoxemic mice and in critically ill patients with surgical sepsis where increased levels correlated with non-survival. In animal models, the blockade of HMGB1 can inhibit the inflammation associated with endotoxemia, cecal ligation and puncture and LPS-triggered acute lung injury. Identification of HMGB1 and similar "late" mediators may provide a broader therapeutic window for successful immune modulating therapy in sepsis.

Role of Host Mediators in the Resolution of Sepsis

Regulatory processes and mediators exist for the purpose of modulation and eventual resolution of inflammation and the septic response. An absence in the decline of proinflammatory mediators such as TNF and IL-6 over the course of sepsis is an associated risk factor for mortality. Monocyte activation results not only in production of proinflammatory cytokines, but also expression of a number of endogenous cytokine antagonists including soluble TNF receptors, the IL-1Ra and additional anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β (TGF-β). IL-10 has multiple anti-inflammatory properties including inhibition of cytokine production from activated monocytes. IL-10 inhibits expression of those cytokines known to contribute to sepsis, as well as important chemokines, including IL-8. In addition, IL-10 increases expression of other anti-inflammatory molecules such as IL-1Ra and soluble TNF receptors. Exogenous administration of IL-10 in various experimental models has been used in an attempt to decrease inflammatory cytokines and diminish organ injury. Human studies showed that patients who did not survive ARDS had lower levels of IL-10 in their BAL fluid compared to survivors. Furthermore, the inability to increase IL-10 in response to meningococcal infection was associated with increased mortality. Thus, IL-10 and additional regulatory cytokines (e.g. TGF-β, IL-13) possess a number of anti-inflammatory properties and are important contributors to the endogenous regulation of the acute septic response.

Role of the Coagulation Cascade in Sepsis

Dysregulation of the coagulation cascade occurs in sepsis as reflected by activation of pro-coagulant pathways, consumption of clotting factors, alterations in fibrinolysis, and reduced anticoagulant activity. A common hematologic alteration in sepsis is the development of disseminated intravascular coagulation (DIC) which is an acquired state of activation of coagulation and intravascular fibrin formation resulting in vascular thrombosis. In addition to proinflammatory cytokines, tissue factor (TF) activation also plays a prominent role in activating the coagulation cascade, initiating fibrin formation and contributing to the development of DIC. Concurrent with enhanced production of fibrin, there is decreased fibrinolysis related to increased plasminogen activator inhibitor type 1 (PAI-1), as well as dysfunction and/or depletion of antithrombin III, protein C, protein S and tissue factor pathway inhibitor (TFPI). AT III which inhibits thrombin by forming thrombin-antithrombin (TAT) complexes is decreased in sepsis related to degradation by elastases from activated neutrophils, dilution secondary to volume resuscitation, and impaired hepatic synthesis. Despite a correlation between low AT III levels and mortality in patients with sepsis, replacement trials of AT III have failed to show a significant effect on improving mortality.

Protein C is also noted to be depleted among patients with sepsis and septic shock. Regulation of activation of protein C to activated protein C (APC) in the coagulation cascade is mediated in a complex manner and will not be discussed here. APC, upon dissociation from its receptor, binds to its co-factor, protein S, to subsequently inactivate factors Va or VIIIa, thus playing a key role in inhibiting coagulation. It is both antithrombotic and profibrinolytic. APC also possesses anti-inflammatory activity. In models of endotoxemia, APC infusion decreases cytokine production and attenuates neutrophil activation. These anti-inflammatory effects appear to be independent of APC's anticoagulant effect. Following

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Important anti-inflammatory molecules include IL-10, IL-1Ra and soluble TNF receptors. IL-10 inhibits expression of proinflammatory cytokines known to contribute to sepsis, as well as important chemokines, including IL-8. In addition, IL-10 increases expression of other anti-inflammatory molecules such as IL-1Ra and soluble TNF receptors.

AT III inhibits thrombin by forming thrombin-antithrombin (TAT) complexes. AT III is decreased in sepsis due to degradation by elastases from activated neutrophils, dilution secondary to volume resuscitation, and impaired hepatic synthesis. Despite a correlation between low AT III levels and mortality in patients with sepsis, replacement trials of AT III have failed to show a significant effect on improving mortality.
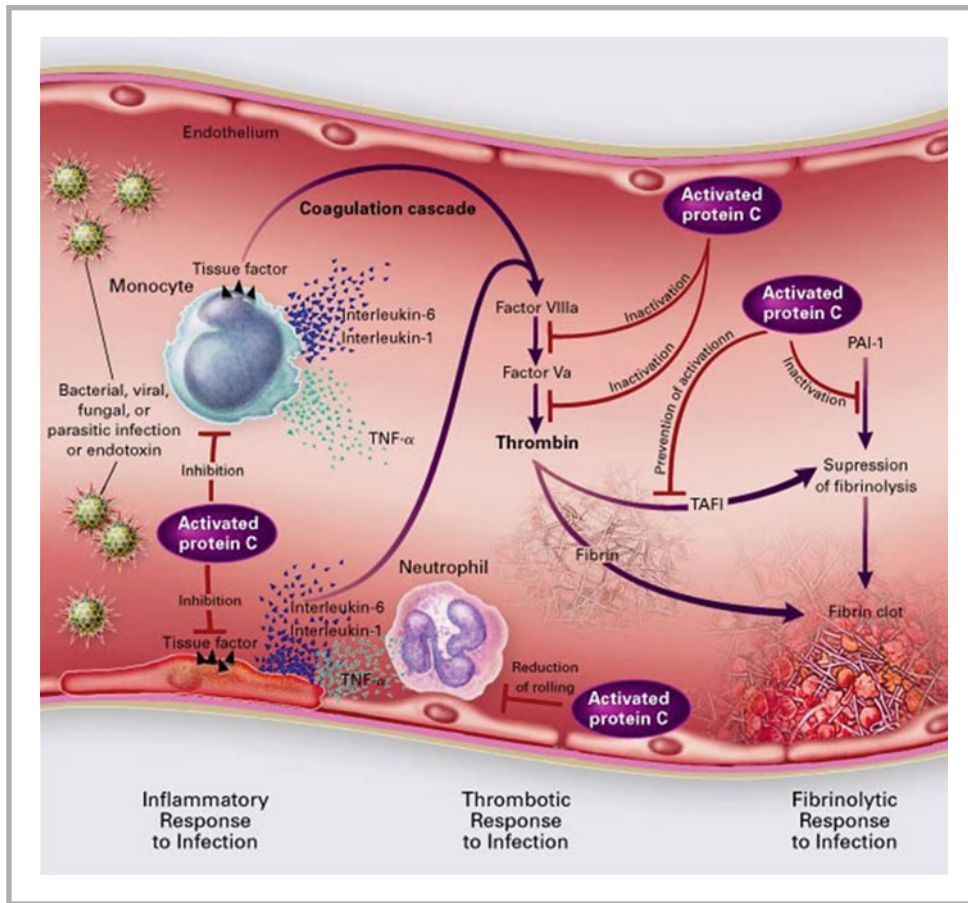
these encouraging pre-clinical studies, clinical trials examining the effect of APC on mortality from sepsis were commenced culminating in the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial. In this study, APC was associated with a statistically significant reduction in 28-day mortality in septic adults. However, a recent pediatric study was stopped after an interim analysis showed that APC administration was highly unlikely to show improvement in outcome (Fig. 27-2).

The administration of activated protein C was associated with a statistically significant reduction in 28-day mortality in septic adults. However, a recent pediatric study was stopped after an interim analysis showed that APC administration was highly unlikely to show improvement in outcome.

Genetic Regulation of the Sepsis Response

It is not uncommon to observe that patients exposed to seemingly identical pathogen insults display strikingly different pathophysiology and outcomes. It is believed that genetic differences among hosts are at least in part responsible for this variability in sepsis responses. As mentioned previously, the insensitivity to LPS in the C3H/HeJ mouse line was mediated by a mutation in the coding sequence for TLR4. Similar findings of an attenuated response to pathogen stimulation have now been reported in patients with mutations in both the TLR4 and TLR2 gene. The polymorphism in TLR2 appears to confer an increased predisposition to severe Gram-positive bacterial infections. More recently, a polymorphism within the CD14 promoter gene (C to T transition at base pair –159) was identified with a particular genotype over-represented among septic shock patients compared to healthy controls. Among the septic patients, the presence of this genotype also was associated with a significantly higher mortality (71% versus 48%). These studies support the concept that genetic alterations in those genes known to participate in the septic response affect the host immune response and likelihood of survival. For a more complete review of the numerous examples of genetic alterations in key inflammatory genes, the reader is directed to the suggested readings.

TREATMENT STRATEGIES

Overview

Treatment of sepsis involves four important components: initial resuscitation, elimination of pathogen, maintenance of oxygen delivery, and carefully directed regulation of the inflammatory response.

As the cellular response to sepsis has become better understood, the approach to treatment of sepsis has become broader. The treatment of sepsis involves four important components: initial resuscitation, elimination of pathogen, maintenance of oxygen delivery, and carefully directed regulation of the inflammatory response. As reviewed above, sepsis is an immunologically complex response to an invasive pathogen necessitating tight physiologic regulation in order to eradicate the organism while maintaining cellular and organ homeostasis. In cases where the immunologic and inflammatory responses continue to escalate, numerous pathways are altered and may ultimately prove amenable to immune modulating therapy, but this approach has been unsuccessful to date.

Initial Resuscitation

The initial priority in the treatment of the septic child is respiratory and cardiovascular stabilization. The primary goals of therapy in those initial hours following clinical presentation are to maintain oxygenation and ventilation, achieve normal perfusion and blood pressure, and re-establish appropriate urine output for age. Children with sepsis may have altered mental status which, if profound, raises concern about the ability to protect the airway. Tachypnea associated with a primary or compensatory respiratory alkalosis is commonly present. The combination of increased lung vascular permeability and aggressive fluid resuscitation to restore intravascular volume and maintain blood pressure may contribute to the subsequent development of pulmonary edema. In children with lung edema, the related changes in lung compliance and loss of functional residual capacity can dramatically increase the work of breathing ultimately necessitating tracheal intubation and mechanical ventilatory support. Arterial blood gas analysis may show hypoxemia and metabolic acidosis; however, the decision to provide mechanical ventilatory support should not be based solely on laboratory findings. The presence of increased work of breathing, hypoventilation or obtundation are all indications for instituting mechanical ventilatory support which holds additional benefit in decreasing the overall oxygen consumption, especially when combined with sedation and paralysis. It should be stated, however, that children with warm shock can commonly be managed without endotracheal intubation so long as they are not obtunded or fluid overloaded. Disorientation or lethargy with intact responsiveness does not require placement of an artificial airway as many institutions manage these patients without intubation. The work of breathing associated with hyperventilation in the absence of pulmonary edema is not clinically significant. Furthermore, there is no evidence that decreasing work of breathing in the presence of distributive shock will result in redistribution of nutrient flow to vital organs, the very nature of distributive shock. However, it is more common for infants to present with cardiac dysfunction and pulmonary edema or seriously altered mental status requiring endotracheal intubation and mechanical ventilation. Correction of intravascular volume depletion should be made prior to the institution of positive pressure ventilation. The decrease in venous return after the initiation of positive pressure ventilation may lead to further hemodynamic compromise in the child with intravascular volume depletion. Caution should also be taken in choosing sedative agents for intubation, using agents that have the least impact on tenuous hemodynamics (e.g. ketamine). Controversy exists over the adrenal suppressive effect of a single dose of etomidate when used for intubation in septic children and adults. The pediatric critical care clinician should be aware of the concern for adrenal suppression following a single dose of etomidate used for the intubation of children with septic shock and the published guidelines which do NOT recommend its use in this setting. Following intubation, attention must be paid to matching the mechanically provided minute ventilation to that which was present during spontaneous respiratory effort so that respiratory compensation of acidemia is preserved. If it is deemed that positive pressure ventilation is not needed, supplemental oxygen should be provided to maintain normal oxygen saturations.

With regard to fluid status, septic children have decreased effective intravascular volume related to a number of causes. Poor oral intake of fluid for a period of time prior to clinical presentation is common. Increased vascular permeability leads to intravascular volume loss due to extravasation of fluid from the vascular space, so-called "third spacing". Finally, the NO-mediated vasodilation reviewed above increases vascular capacitance thereby decreasing the effective circulating volume. Thus, when sepsis is suspected, it is imperative to expeditiously achieve vascular access and initiate fluid resuscitation with 20 mL/kg of isotonic fluid as quickly as possible. While debate continues as to the most effective fluid for resuscitation, no pediatric literature exists to support colloid over crystalloid, the latter of which was recently demonstrated to be equally effective in a large adult ICU trial. There is some support for using colloid fluid in patients with a narrow pulse pressure; however, this practice is not supported by any large, well-designed clinical studies.

While following the clinical exam for signs of intravascular volume overload (new onset of rales, increased work of breathing, development of a gallop, or hepatomegaly), fluid should be administered quickly with the goal of monitoring heart rate response, urine output, capillary refill time and level of consciousness. Initial fluid resuscitation of the child with septic shock commonly requires a volume of up to or greater than 60 mL/kg in the first hour and one retrospective study demonstrated an increased survival in children given fluid volumes of 40 mL/kg or more within the first hour. The ACCM Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock recommend that the child with septic shock be repeatedly examined for the development of "rales, gallop rhythm, hepatomegaly, and increased work of breathing" during volume loading, and that in the absence of such findings, volumes up to 200 mL/kg can be administered in the first hour. These guidelines further state that "the rate of fluid administration should be reduced substantially when there are clinical signs of adequate cardiac filling without hemodynamic improvement."

> Adequate volume resuscitation of the child with septic shock commonly requires a volume of up to or greater than 60 mL/kg in the first hour.

Despite on-going fluid resuscitation, hypotension and inadequate organ perfusion may persist requiring the initiation of inotropes and/or vasopressors. In children, vasoactive medicines should only be given in addition to fluid resuscitation. However, consensus guidelines recommend that vasoactive infusions may be necessary in some cases to sustain perfusion pressure even when hypovolemia is not yet resolved. Dopamine is the most common first choice agent selected for hemodynamic support in those patients with fluid-refractory shock. Dopamine provides inotropic support at lower concentrations; however, it is often necessary to increase it to higher doses that provide vasopressor activity (up to 20 μg/kg/min) to maintain adequate tissue perfusion. The decision of which agent to add in the setting of dopamine-refractory shock should be based on the underlying cause of cardiovascular compromise. For example, if hemodynamic instability is related to low cardiac output from direct cardio-depressant effects then increased inotropy from dobutamine or low-dose epinephrine may be indicated. If hypotension persists secondary to decreased vascular tone, then agents such as epinephrine and norepinephrine dosed in the alpha agonist range should be considered. Finally, in children who demonstrate low cardiac output and/or increased afterload from vasoconstriction (i.e. increased systemic vascular resistance), agents with primarily inotropic or vasodilator function including milrinone, dobutamine or short-acting nitrovasodilators can been considered in the fluid-resuscitated, normotensive child. As in evaluating the adequacy of fluid resuscitation, similar clinical parameters should be followed in titrating vasoactive medications. Appropriate endpoints include: capillary refill time less than 2 s, normal peripheral pulses, warm extremities, urine output greater than 0.5 mL/kg/h, improved mentation, resolving acidemia, decreasing serum lactate and when available, superior vena cava (SVC) oxygen saturation greater than 70%. Invasive monitoring can further assist the clinician with goal directed endpoints.

> Appropriate endpoints of sepsis resuscitation include: capillary refill time less than 2 s, normal peripheral pulses, warm extremities, urine output greater than 0.5 mL/kg/h, improved mentation, resolving acidemia, decreasing serum lactate and when available, superior vena cava oxygen saturation greater than 70%.

Invasive Monitoring

Although frequent beside examination remains integral to the care of the child in septic shock, an additional task in the initial resuscitation phase is placement of appropriate and necessary vascular access and monitors. Central venous access is a necessity for the child with fluid refractory shock to provide for delivery of vasoactive medicines and large volumes of fluid. These catheters can be useful for following the central venous pressure (CVP) during fluid

administration. Finally, when the tip is located in the superior vena cava, blood sampling can provide an approximate measure of the mixed venous oxygen saturation which has been validated as a critical target in adult shock resuscitation. The decision regarding the access site for a central venous catheter is dictated by a number of mitigating factors such as the experience level of the operator and the presence of coagulopathy. Femoral catheters, in the absence of abdominal pathology, can be used to estimate CVP with good correlation. The CVP measured in the abdominal inferior vena cava must be assessed carefully as a low CVP can be a reliable indicator of hypovolemia, however, a normal or high CVP in the presence of abdominal distention does not automatically exclude the presence of hypovolemia. Multiple adult studies have demonstrated that even an accurate intra-thoracic CVP may be a poor approximation of left ventricular end diastolic pressure and volume. The CVP can be elevated despite the presence of hypovolemia if pulmonary hypertension, right ventricular dysfunction with poor diastolic compliance, tricuspid regurgitation, cardiac tamponade or an intracardiac left-to-right shunt exists. Even though precise determination of the true mixed venous saturation requires the presence of a pulmonary artery catheter, the approximations derived from the SVC saturation have proven a useful target in septic adults. In contrast, because of differences in oxygen extraction between the upper extremities, abdomen, and lower extremities, venous oxygen saturations from a low lying femoral line do not accurately correlate with those measured in the pulmonary artery. Consensus guidelines recommend therapeutic endpoints of superior vena cava oxygen saturation >70% or mixed venous (pulmonary artery) oxygen saturation >65%.

Placement of an intra-arterial catheter provides continuous monitoring of systemic blood pressure, pulse pressure and hemodynamic variation with respiration, as well as a means for drawing arterial blood gases, lactate levels and additional laboratory studies. The arterial blood also provides the most accurate measure of arterial oxygen content and can be used to both assess the function of the lungs and to maximize oxygen delivery. In the ventilated patient, variation in the amplitude of the arterial waveform has been found to correlate closely with intravascular volume status (see also Chapter 3). Systolic pressure variation (SPV), also referred to as "reverse pulsus paradoxus," is the variation in beat-to-beat amplitude of the arterial pulse during positive pressure ventilation. A single positive pressure breath normally affects the arterial pressure in a biphasic manner. The initial response to a positive pressure breath is to "squeeze" pulmonary vascular blood into the left atrium (the opposite, "pooling" of blood, occurs with negative pressure inspiration) leading to a rise in systolic pressure. In addition, positive intrathoracic pressure reduces the afterload on the left ventricle by virtue of the pressure gradient from the thorax outward further augmenting this early rise in arterial pressure. These two effects produce an upward movement of the systolic blood pressure coincident with the positive pressure breath, referred to as the Δ up component of SPV. Following this Δ up, a fall in systolic pressure occurs a few beats later as the decreased venous return (preload) to the right ventricle that occurred during positive pressure inspiration is now evident as decreased preload to the left ventricle after a few cardiac cycles. The transient reduction in right ventricular volume and output leads to a smaller left ventricular stroke volume and a brief reduction in arterial pressure that occurs later in the ventilator cycle (Δ down).

| An exaggerated SPV (>10 mm Hg) is seen early in the setting of hypovolemia.

An exaggerated SPV (>10 mm Hg) has been seen early in the setting of hypovolemia. This is due to a greater Δ down component. Several studies have shown that an increase in the SPV occurs prior to a fall in arterial pressure and may a better predictor of hypovolemia than a low pulmonary capillary wedge pressure (PCWP) (<10 mm Hg). An increase in the SPV due to a greater Δ down component can also occur due to high airway pressures causing decreased venous return.

Recently, pulse pressure variation (PPV) has also been found to be a sensitive indicator of preload, and more importantly, fluid responsiveness. PPV is defined as the maximal pulse pressure (systolic minus diastolic blood pressure) less the minimum pulse pressure divided by the average of these two pressures.

The use of systolic pressure variation and pulse pressure variation is limited to those patients on mechanical ventilation. These measurements should occur when there is no spontaneous breathing. In the presence of a consistent delivered tidal volume, systolic pressure variation can be used to track the adequacy of intravascular volume over time (Fig. 27-3).
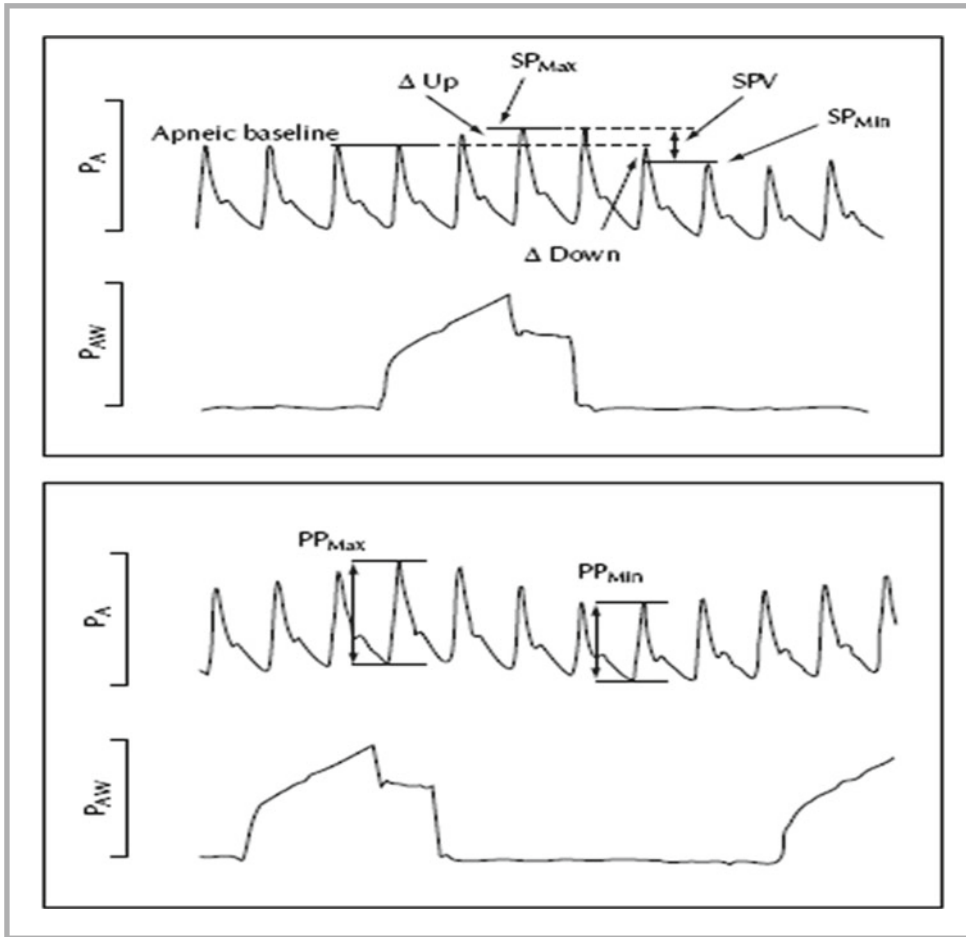
The decision to use a pulmonary catheter (PAC) with the goals of optimizing left ventricular preload, monitoring cardiac index and measuring oxygen delivery remains controversial. Caveats to interpretation of PAC data include the presence of an intracardiac shunt and an abnormally functioning mitral valve or other obstructed left heart lesion as either shunting, regurgitation, or inaccurate pressure determinations will alter cardiac index and/or the pulmonary capillary wedge pressure measurements. As previous data in adults have shown no benefit of PAC use, a recent consensus statement regarding their use stated that the role of PAC remains unclear. Studies of children with septic shock have shown that the information obtained from a PAC aided in identifying hemodynamic profiles different from those presumed by care givers and has directly influenced care decisions. It was concluded by a recent consensus panel to be of potential benefit in improving the management of pediatric patients. Pulmonary artery catheter placement should be considered for pediatric patients who remain in shock after resuscitation and initiation of the usual vasoactive agents in whom the fluid status and cardiac function remains unclear. In this setting, therapeutic endpoints are a cardiac index of >3.3 and <6.0 L/min/M^2 and systemic and pulmonary vascular resistances within the normal range.

Elimination of Pathogen

Early identification of a possible offending pathogen and aggressive source control represent a crucial component of septic shock therapy. Prompt initiation of appropriate antimicrobial therapy against the causative pathogen has been shown to be one of the most important predictors of outcome. In a 1980's study of over 1,100 adults, providing appropriate

antimicrobial coverage at least 1 day prior to identification of the organism was associated with improved survival. The pathogen itself has prognostic significance. Fungal infections, while accounting for only a minority of sepsis cases, carry the lowest survival rate, followed by Gram-positive and Gram-negative bacteria. Survival rate has been reported to be the highest in patients in whom no pathogen was identified.

Because of the importance of appropriate antimicrobial therapy, the decision of which agents to empirically start must balance potential side effects versus maximizing coverage. In this respect, it is important to be familiar not only with the most common causative pathogens, but also the local ICU nosocomial risks and pathogen resistance patterns. Initially, broad antibiotic coverage is initiated. Neonates are most frequently placed on ampicillin and an aminoglycoside (e.g. gentamicin) or a third generation cephalosporin such as cefotaxime. In infants and children over the age of 4–6 weeks, the decision to start vancomycin empirically should be considered in light of the increasing antibiotic resistance of *Streptococcus Pneumoniae* and rising incidence of community acquired Methicillin Resistant *Staphylococcus Aureus* (MRSA). In addition, a 3rd or 4th generation cephalosporin (e.g. ceftriaxone) should be used. Suspicion of a Gram-negative infection or nosocomial infection requires additional coverage, usually in the form of an aminoglycoside, for the possibility of *Pseudmonas* species and other resistant Gram-negative organisms. Because of its broad coverage, including many anaerobic species, and low renal toxicity, piperacillin/tazobactam is empirically administered with increasing frequency. The antiviral agent, acyclovir, should be administered if there is suspicion of a herpes virus infection. In immunocompetent children, the decision to start empiric antifungal therapy remains controversial. In the child who is not improving over the initial days of empiric coverage or in whom there is a higher risk for fungal infection (e.g. presence of indwelling devices, immunosuppression or other significant co-morbidities), antifungal coverage may be indicated. The development of agents equally as effective as amphotericin, but with substantially reduced nephrotoxicity such as fluconazole and caspofungin, may ultimately sway the risk/benefit analysis towards more aggressive, earlier initiation of empiric antifungal coverage in select, high risk populations. The ability to narrow the spectrum of treatment once the causative organism has been identified will reduce the number of potential side effects and curtail the development of pathogen resistance related to imprudent use of broad spectrum antibiotics.

Maintenance of Oxygen Delivery

The current mainstay of supportive care in sepsis remains the maintenance of adequate oxygen delivery in the face of myocardial depression, capillary leak, acidosis, and massive cytokine release. While some early adult studies have suggested improved outcomes when achieving supra-normal levels of oxygen delivery, this approach in pediatric sepsis remains unproven. This is likely due to the fact that septic patients may have a perturbed ability to extract oxygen in addition to suboptimal oxygen delivery. Clinically, this impairment in cellular oxygen uptake may be reflected by an inappropriately high central venous oxygen saturation ($S_{cv}O_2$) in the face of a progressive and therapy refractory acidosis. Optimizing appropriate oxygen delivery remains a clinical goal and incorporates the need for maximizing oxygen carrying capacity. While there is no recommended hemoglobin level for children, the most recent NIH consensus conference suggested a hemoglobin concentration of 10 g/dL for adults with cardiopulmonary compromise as part of a protocol toward achieving the therapeutic goal of $S_{cv}O_2$ >70%, with improved outcomes demonstrated when this goal was achieved during initial resuscitation. In the context of fluid loading with blood transfusion, empiric administration of diuretics to eliminate extra fluid should be avoided until hemodynamic stability has been achieved or if the child exhibits signs of intravascular volume overload defined earlier in this chapter. Similar clinical parameters can be assessed in response to blood transfusion. Perhaps the best assessments are determinations that provide indirect evidence of the balance between oxygen delivery and consumption such as lactate levels and mixed venous oxygen saturation.

In the context of fluid loading with blood transfusion, empiric administration of diuretics to eliminate extra fluid should be avoided until hemodynamic stability has been achieved or if the child exhibits signs of intravascular volume overload.

Finally, the nutritional status of the septic child must be addressed. Patients with sepsis often have poor nutrition prior to admission to the PICU and often may not be fed in the first few days of illness. This state combined with the increased metabolic rate associated with sepsis place the septic patient at risk for protein calorie malnutrition. Intestinal hypoperfusion in combination with absence of local enterocyte nutrition can cause mucosal barrier dysfunction and may contribute to translocation of bacteria and endotoxin from the intestine into the blood stream. While the use of enteral feeding in critical illness has been shown to improve survival and decrease hospital stay, its use must be balanced with the risk of stressing intestinal function in the face of poor splanchnic perfusion, especially in the child requiring the use of vasopressors such as epinephrine and norepinephrine. Regardless of which mode of nutrition is chosen, the goal of achieving nitrogen balance is important for allowing recovery and return to physiologic homeostasis. In the absence of enteral feedings, protection from stress-related gastrointestinal ulcer formation is advised.

Additional Therapeutic Modalities

Because poor outcome in sepsis has been attributed to a dysregulated proinflammatory state, anti-inflammatory agents, such as corticosteroids, have long been proposed as a potential therapeutic strategy. Anecdotally, it has been observed that some patients treated with antibiotics appear to acutely worsen in a time frame consistent with the onset of antibiotic activity. This observation has been attributed to massive release of bacterial products following the lysis of high numbers of bacteria. To this end, investigators had shown that animals treated with anti-inflammatory drugs prior to receiving antibiotics demonstrated a less severe response to bacterial lysis. Despite encouraging preclinical studies, two subsequent large adult trials using high dose steroids early in sepsis showed no improvement in mortality. More recently, studies using lower doses of steroids over a longer period of time have suggested a possible benefit including a reduced time to cessation of vasopressor therapy. These more recent observations have stimulated a resurgence in the use of corticosteroids in sepsis. Adrenal insufficiency is frequently unrecognized in children with septic shock and a low basal circulating cortisol level, especially in association with an abnormal corticotropin stimulation test, has been associated with higher mortality rates. Therefore, identifying "at risk" patients with a corticotropin stimulation test and treating this group may improve outcome in sepsis. A study in which adult septic shock patients who were classified as "nonresponders" based on corticotropin stimulation results were treated with hydrocortisone and fludrocortisone for 7 days and had a significantly reduced risk of death. However, this initial observation was not observed in larger follow-up studies. Thus, the use of hydrocortisone and the application of a corticotropin stimulation test in septic patients remains highly controversial. In pediatrics, it is currently recommended that any child with fluid- and catecholamine-refractory shock (inadequate response to two or more vasoactive agents), has a known history of adrenal insufficiency, or has previously received exogenous steroids should be considered for steroid replacement with hydrocortisone (usual dose between 50 and 100 mg/M^2/day divided every 6 h).

Because the host response to sepsis is mediated by circulating inflammatory molecules, it has been hypothesized that extracorporeal removal of these mediators via hemofiltration or exchange transfusion may affect outcome. Case reports suggest that arterial oxygenation and hemodynamics can be improved with use of hemofiltration during sepsis and multiple organ failure. However, there exist many mitigating factors in evaluating the pediatric experience and the efficacy of hemofiltration remains unproven. Challenges with instituting extracorporeal hemofiltration include difficulty with vascular access in smaller children, potential fluid and electrolyte imbalance, hypothermia, anticoagulation requirements and acutely compromised hemodynamics during initiation. In addition, it is not known whether beneficial proteins such as albumin, immunoglobulins, clotting factors and counter-regulatory cytokines are removed during this process. While experience shows that hemofiltration can be safely performed in children with sepsis, it remains unclear if it will improve outcome.

Part of the inflammatory response involves cytokines that cause widespread activation of the coagulation cascade with suppression of fibrinolysis as reviewed above. It is encouraging

Adrenal insufficiency is frequently unrecognized in children with septic shock. A low basal circulating cortisol level, especially in association with an abnormal corticotropin stimulation test, has been associated with higher mortality rates.

that administration of activated protein C in adults with septic shock was associated with a significant decrease in 28-day mortality. Though activated protein C should not be routinely used in pediatric sepsis, indications for its use may be determined from further trials in pediatric sepsis. In the meantime, many other potential immune modulating therapeutic agents have been identified and are currently under investigation. Unfortunately, many of the anti-inflammatory agents tried to date (anti-IL-1, anti-bradykinin, anti-endotoxin, anti-TNF-α, soluble TNF receptor and anti-platelet activating factor) have not shown any benefit in large, randomized clinical trials. It is hoped that improvements in study design which include thoughtful stratification of patients, timely identification of the presence or absence of a pathogen and consideration of genetic factors that influence outcome will eventually assist in discovering and targeting pharmacologic agents that ultimately improve the outcome of the pediatric patient with septic shock.

SUMMARY

Sepsis remains one of the most pressing clinical challenges for the pediatric intensivist. It is apparent that while a great deal is now understood about the biological and molecular mechanisms involved in sepsis, this knowledge has not yet had a dramatic impact on improving outcome. At present, therapeutic modalities for sepsis remain largely supportive and founded on the fundamental physiologic principle of providing adequate oxygen delivery. With this approach, mortality in pediatric sepsis improved modestly over the past decades. However, the fact that over 4,000 children per year continue to die in association with severe sepsis argues that further advances be made. Realization of the goal of improving survival requires investigators committed to achieving further mechanistic insights into the physiologic, molecular, and genetic biology of sepsis, in concert with large pediatric-specific interventional trials.

REVIEW QUESTIONS

1. **In comparison to adults, children are more likely to present with which one of the following hemodynamic profiles?**
   A. High cardiac index with high systemic vascular resistance
   B. High cardiac index with low systemic vascular resistance
   C. Low cardiac index with high systemic vascular resistance
   D. Low cardiac index with low systemic vascular resistance
   E. Normal cardiac index with low systemic vascular resistance

2. **Activation of the innate immune system in Gram-positive bacterial sepsis is mediated by:**
   A. Toll-like receptor 2 (TLR2)
   B. TLR3
   C. TLR4
   D. TLR5
   E. TLR6

3. **Which of the following biologic effects is most accurately attributed to TNF-α?**
   A. Induction of nitric oxide synthase (iNOS)
   B. Inhibition of adhesion molecules and chemokines that facilitate leukocyte-endothelial cell adhesion
   C. Inhibition of IL-1β
   D. Inhibition of tissue factor
   E. Upregulation of protein C

4. **Which of the following statements regarding IL-1β is true?**
   A. IL-1β decreases tissue factor expression
   B. IL-1β increases adhesion molecule expression
   C. IL-1β inhibits monocyte activation and phagocytosis
   D. IL-1β is the only agonist among the IL-1 family of proteins
   E. IL-1β stimulates thrombomodulin secretion

5. **Which of the following biologic mediators is an anti-inflammatory cytokine?**
   A. IL-1β
   B. IL-6
   C. IL-8
   D. IL-10
   E. TNF-α

6. **Which of the following cytokines functions primarily as a chemokine?**
   A. IL-1β
   B. IL-6
   C. IL-8
   D. IL-10
   E. TNF-α

7. **Which of the following statements best summarizes the biologic effects of Protein C?**
   A. Antithrombotic and anti-inflammatory
   B. Antithrombotic and proinflammatory
   C. Antithrombotic, but without any effect on the inflammatory process
   D. Prothrombotic and anti-inflammatory
   E. Prothrombotic and proinflammatory

8. **Once stable oxygenation and ventilation are assured, the most important priority in the patient with septic shock is:**
   A. Adequate sedation and paralysis
   B. Fluid resuscitation with 20 mL/kg of isotonic fluid
   C. Initiation of inotropic support
   D. Placement of an arterial catheter
   E. Placement of central venous access

9. **A 5 year old female is admitted to the pediatric intensive care unit with septic shock. She is well oxygenated on a 40% oxygen face mask. She has already received 60 mL/kg of 0.9% normal saline and has been started on a dopamine infusion at a rate of 5 mcg/kg/min. In monitoring her response to these interventions, which of the following should NOT be used as a therapeutic endpoint to monitor her progress?**
   A. Capillary refill time
   B. Echocardiographically measured ejection fraction
   C. Mental status
   D. Serum bicarbonate level
   E. Urine output ≥1 mL/kg/h

10. **A 12 year old male with acute lymphocytic leukemia is admitted to the pediatric intensive care unit with vancomycin resistant enterococcus bacteremia. His vital signs reveal a temperature of 39.6°C, a heart rate of 145 bpm, a respiratory rate of 20 breaths/min, and a blood pressure of 108/35 mm Hg. He is lethargic, but arousable. His pulses are bounding and his capillary refill is brisk. An arterial blood gas reveals a pH 7.31, a $PaCO_2$ 33 mm Hg, a PaO_2 65 mm Hg, an oxygen saturation of 93%, and a base deficit of (−10). The oxygen saturation of venous blood sampled from the superior vena cava is 88%.**

Which of the following statements best describes his clinical condition?
   A. The young man is bacteremic, but not in shock as evidenced by his bounding pulses, brisk refill, and normal systolic blood pressure.
   B. The young man is in shock with inadequate oxygen extraction at the tissue level evidenced by the elevated superior vena cava saturation.
   C. The young man has a primary metabolic acidosis, but has a normal oxygen extraction as oxygen saturation in the superior vena cava is normally higher than elsewhere in the body.
   D. The young man has a primary metabolic acidosis, but is not in shock, evidenced by his high superior vena cava saturation.
   E. The young man has a primary respiratory alkalosis that would benefit from supplemental oxygen therapy.

11. **There is sufficient data to justify the use of which of the following adjuvant therapies in pediatric sepsis?**
   A. The administration of activated protein C to a child in septic shock without thrombocytopenia or coagulopathy
   B. The administration of anti-TNF-α monoclonal antibodies to a septic patient to decrease the proinflammatory response
   C. The administration of stress dose hydrocortisone to a septic patient whose serum cortisol level fails to increase sufficiently in response to a corticotropin stimulation test
   D. The early initiation of high volume, continuous veno-venous hemofiltration to remove proinflammatory cytokines
   E. The transfusion of packed red blood cells to maintain a hemoglobin ≥12 g/dL in order to provide supranormal oxygen delivery

12. **It has become clear that dysregulation of the coagulation cascade occurs in sepsis as reflected by activation of procoagulant pathways, consumption of clotting factors, alterations in fibrinolysis, and reduced anticoagulant activity. Which of the following components of coagulation is increased during sepsis?**
   A. Antithrombin III (AT III)
   B. Plasminogen activator inhibitor type 1 (PAI-1)
   C. Protein C
   D. Protein S
   E. Tissue factor pathway inhibitor (TFPI)

ANSWERS

1. C
2. A
3. A
4. B
5. D
6. C

7. A
8. B
9. B
10. B
11. C
12. B

SUGGESTED READINGS

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