Sepsis

8

Lexie H. Vaughn and Jeffrey S. Upperman

8.1 Introduction Including Definition and Incidence

Sepsis is a major cause of morbidity and mortality in the United States, accounting for over 720,000 hospitalizations annually. Despite recent advances in neonatal and pediatric critical care medicine, the number of children suffering from sepsis continues to rise, and sepsis remains the leading cause of death in children worldwide. A retrospective review of observational cohort datasets from 1995, 2000, and 2005 demonstrated an 81% increase in cases of severe sepsis in patients aged 19 years or younger over the ten-year period. Notably, the prevalence of sepsis is significantly higher in infants and newborns than in older children.

The most common pathogens identified in the pediatric and adult populations include *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella*, and *Bacteroides* species. The most common organisms found in neonates within the first 72 hours of life are group B streptococci and *E. coli*.

L. H. Vaughn
Department of General Surgery, Vanderbilt University Medical Center, Nashville, CA, USA
e-mail: lexie.h.vaughn.1@vumc.org

J. S. Upperman (✉)
Department of Pediatric Surgery, Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, CA, USA
e-mail: jeffrey.upperman@vumc.org

In the adult population, sepsis is defined as life-threatening organ dysfunction in a patient with a suspected infection. Former criteria for defining the clinical signs and symptoms of the systemic inflammatory response syndrome (SIRS) focused on the inflammatory response of the host and defined a continuum of clinical progression from SIRS to sepsis to shock. This definition has fallen out of favor since 2016, with the publication of Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). SIRS criteria have now been replaced in the clinical setting by the Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) as a metric of organ dysfunction. This new scoring system accompanies a new definition of sepsis, which emphasizes the dysregulated host response to infection as the primary cause of sepsis and organ dysfunction in a patient with a suspected infection. The predictive validity of in-hospital mortality for adult ICU patients has been demonstrated to be significantly greater for SOFA than the former SIRS criteria. Despite these reassuring results, the SOFA score and updated definition of sepsis were developed based on adult patients only and do not take into account differences in baseline physiology and responses to insult in children and neonates.

In children and neonates, sepsis is still defined based on SIRS criteria as a triad of fever, tachycardia, and vasodilation with a change in mental status or prolonged capillary refill >2 seconds

P. Puri, M. E. Höllwarth (eds.), *Pediatric Surgery*, https://doi.org/10.1007/978-3-030-81488-5_8

(Alaedeen et al. 2006). There has not yet been a generalized transition to scoring systems for organ dysfunction in the clinical setting as seen in the adult population; however, some predictive scoring systems do exist for the pediatric population. Leclerc et al. reported excellent predictive validity of in-hospital mortality in pediatric ICU patients using the Pediatric Logistic Organ Dysfunction-2 (PELOD-2). This tool was originally proposed in 2005 and updated in 2013, and it incorporates Glasgow coma score (GCS), systolic blood pressure (SBP), mean arterial pressure (MAP), and heart rate (HR). While there has been no generalized consensus regarding the use of this tool, much like the SOFA score in adults, it shows promise as a diagnostic tool for pediatric sepsis.

Children with sepsis and progressive septic shock present a unique set of challenges for clinicians. The diagnosis and management, specifically the initial fluid resuscitation and subsequent hemodynamic support, are different than in the adult population due to differences in baseline physiology and changes that occur as children age.

8.2 Risk Factors

8.2.1 Barriers to Infection

The human body is colonized by a variety of nonpathogenic microorganisms. These normal florae adhere to the epithelial lining and prevent the attachment of other pathogenic microbes. Additional protective mechanisms, such as intestinal peristalsis, gastric acid secretion, and immunoglobulins, help to limit pathologic microbial invasion (Table 8.1). Oropharyngeal, nasopharyngeal, tracheobronchial, and gastrointestinal secretions are rich in immunoglobulins, which help to prevent bacterial attachment to the epithelium. Specifically, immunoglobulin A (IgA) binds microorganisms at the epithelial surface, thereby impairing attachment to the epithelial lining—a critical step in the establishment of infections.

Table 8.1 Defense mechanisms against microbial invasion

Host defense	Actions
Gastric acid	Lower pH promotes a hostile environment for bacterial growth
Peristalsis	Coordinated movements sweep the bacteria downstream, limiting attachment to the mucosa
Local flora	Indigenous microbial flora prevents the overgrowth of pathogenic Gram-negative bacteria
Immunoglobulin	IgA coats and aggregates bacteria and prevents their attachment to intestinal mucosa
Mucus	Intestinal mucus forms a thick barrier, which prevents bacterial attachment

Any breach in the mucosal barrier permits bacteria or viruses to infiltrate the epithelial lining and elicit an inflammatory response. For instance, trauma, surgery, malnutrition, burns, immunosuppression, shock, and reperfusion injury following an ischemic event can cause gut barrier failure. Following reperfusion injury, inflammatory cells elaborate toxic reactive oxygen species, such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2), which damage the epithelial lining and permit the translocation and internalization of microbes.

8.3 Pathophysiology of Sepsis

Figure 8.1 summarizes the pathogenesis of the systemic inflammatory response syndrome (SIRS) and the immune components involved.

8.3.1 Bacterial Virulence

The most common pathogens identified in children are bacterial in origin. Establishment of a clinical bacterial infection in the host begins with the attachment of the microbe to the epithelial surface of the host, followed by subsequent internalization. The internalized microbe must then evade the local cellular and humoral host defense mechanisms in order to cause infection, multiply,

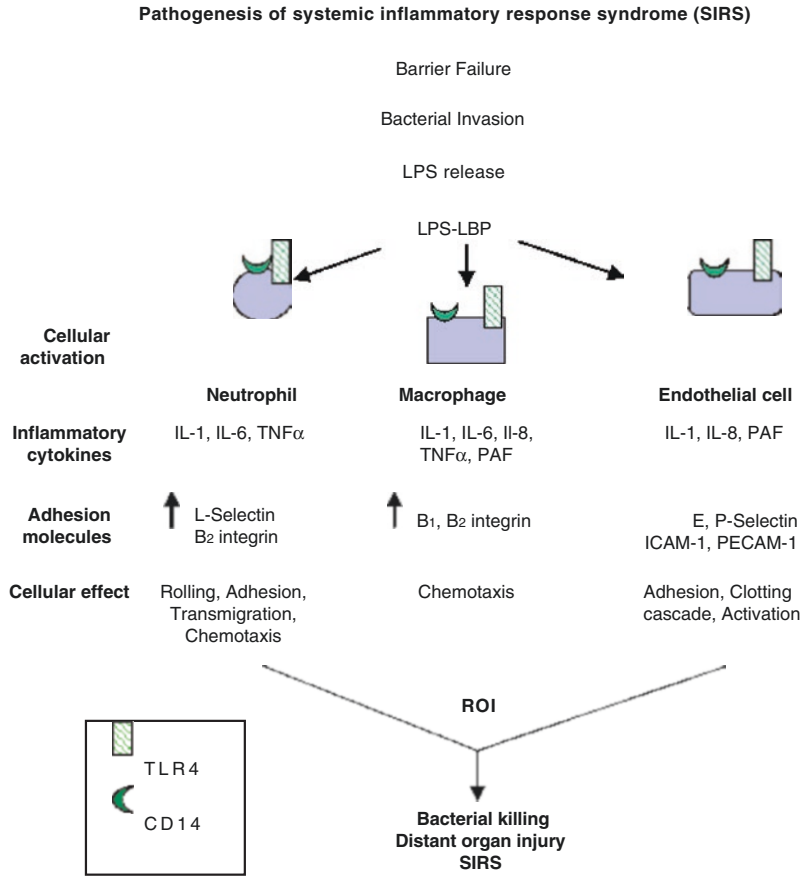

Fig. 8.1 Pathogenesis of systemic inflammatory response syndrome (SIRS). Bacterial invasion secondary to barrier failure leads to the local release of lipopolysaccharide (LPS), with consequent formation of an LPS–lipopolysaccharide-binding protein (LBP)–CD14–Toll-like receptor 4 (TLR4) complex on neutrophils, macrophages, and endothelial cells, resulting in cellular activation. Inflammatory cytokines are released, upregulate adhesion molecules, and promote chemotaxis of neutrophils and macrophages. The activated cells release microbicidal agents typically designed for bacterial killing, but they may be injurious and promote distant organ injury and SIRS if the inflammatory process is "uncontrolled." *ICAM* intercellular adhesion molecule, *IL* interleukin, *MCP* monocyte chemotactic protein, *MIP* macrophage inflammatory protein, *NO* nitric oxide, *PAF* platelet-activating factor, *PECAM* platelet-endothelial cell adhesion molecule, *ROI* reactive oxygen intermediate (or species), *TNF* tumor necrosis

damage local tissue, and elicit an inflammatory response. This is a process that depends largely on microbial virulence factors.

The process of bacterial adherence requires interaction between specific cell surface receptors on the host and key molecules on the pathogen, called adhesins. Bacterial fimbriae or pili are known to promote bacterial adherence to mucosal surfaces. *E. coli* expresses different types of fimbriae that permit their attachment to the D-mannose receptor on epithelial cells. Some microbes also display adhesins that facilitate entry into the host. Indirectly, the host secretes proteins that have a common peptide sequence Arg-Gly-Asp, such as fibronectin, laminin, collagen, and vitronectin, which enhance bacterial attachment to the host.

Once the microbe has attached to the cell surface, the organism may gain entry into the cell through a process called internalization. This requires high-affinity binding between the microbe's pili and cell surface receptors. The cell

surface contains a receptor called integrin, which binds the bacterial pili. The affinity of the pili for this receptor determines whether the microbe attaches to the cell and becomes internalized. Bacterial internalization takes place through phagocytosis. The internalized bacteria are transported in intracellular vesicles known as endosomes or phagosomes.

Once the bacteria have evaded the initial host defense mechanisms and entered the cell, they must survive within the intracellular milieu to establish an infection. Fusion of the cell's lysosome with the phagosome leads to acidification of the phagolysosome complex and neutralization of the internalized bacteria by specific toxins such as hyaluronidase, collagenase, proteinase, deoxyribonuclease, and lecithinase. The bacteria may counterattack by secreting exotoxins to help neutralize the host defense mechanisms. For instance, *S. aureus* produces catalase, which neutralizes hydrogen peroxide. Streptolysin, a streptococcal exotoxin, can inhibit neutrophil migration and impair phagocyte cytotoxicity. One of the most potent bacterial toxins is called lipopolysaccharide (LPS) (or endotoxin). It contains an O-specific side chain, a core polysaccharide, and an inner lipid A region. The lipid A region is a highly potent stimulator of the inflammatory response. This molecule may initiate septic shock by stimulating the release of inflammatory mediators such as arachidonic acid and leukotrienes, or through complement activation. Endotoxin, alone, is sufficient to induce shock when given experimentally to laboratory animals or to human volunteers.

8.3.2 Microbiome

The human microbiome and specifically the native microorganisms found in the human intestine play a significant role in immune regulation and in the pathogenesis of some diseases. The intestine is sterile in utero but becomes colonized at birth and diversifies quickly and significantly in the neonatal period. Recent evidence has suggested that disruption in the microbiome may increase the risk of sepsis and progression to end-organ dysfunction, specifically in the neonatal population. Several mechanisms for this increased risk have been proposed, including selective proliferation of pathologic bacteria secondary to antibiotic use, proinflammatory host immune response, and decreased production of short-chain fatty acids. Changes in the microbiome during critical illness may also impact the host response, increase the risk of end-organ dysfunction, and ultimately impact the clinical course of a patient with sepsis. With increasing accessibility of culture-independent methods for microbial identification, there are potential therapeutic molecular targets for patients with sepsis; however, prospective data in humans are currently limited, and additional investigation is needed.

8.3.3 Neutrophils

Neutrophils are terminally differentiated effector cells that constitute the first line of defense in response to infection or tissue injury. The neutrophil contains proteolytic enzymes and reactive oxygen species that can cause local tissue damage when released into the extracellular matrix. After a 14-day development in the bone marrow, the neutrophils circulate in the bloodstream for 6–14 h. Nearly 50% of the circulating neutrophils attach or adhere to the vascular endothelium—a process known as margination. If there are no detectable infections, the neutrophils undergo apoptosis, or programmed cell death, in the liver or the bone marrow. The neutrophils that adhere to the vascular endothelium must leave the bloodstream through a process known as diapedesis to reach the tissues. There, they can survive for another 48 h performing critical functions such as phagocytosis and microbial killing. Adhesion molecules, such as selectins, integrins, and the immunoglobulin superfamily, govern the adherence of neutrophils to the vascular endothelium. (L)-selectin (CD62L) on the neutrophil surface binds to endothelium (E)-selectin and platelet (P)-selectin, which is upregulated when the endothelial cells are activated by injury, infectious agents, or inflammatory mediators. Migration of

the neutrophil to the site of injury is regulated by a class of molecules known as integrins, which are expressed on the neutrophil surface. Specifically, binding of β_2 integrin to intercellular adhesion molecule 1 (ICAM-1) on the endothelial cell directs neutrophil traffic.

LPS can affect neutrophil adhesion and migration by stimulating the release of tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interferon-γ (IFN-γ), which are known to upregulate ICAM-1 and E-selectin. Lipopolysaccharide binding protein (LBP), a 58-kDa acute phase reactant that is synthesized in the liver, enhances the sensitivity of monocytes and granulocytes to LPS by facilitating binding of LPS to the CD14 cell membrane molecule and to Toll-like receptor 4 (TLR-4) on the surface of neutrophils and monocytes. This interaction upregulates β_2 integrin CD11b/CD18 and enhances the neutrophil–endothelial interaction. Clinically, patients with leukocyte adhesion deficiency are susceptible to recurrent bacterial infections due to the lack of β_2 integrin receptor CD11b/CD18, which results in the inability of the neutrophil to adhere to the endothelium and effect bacterial killing.

Migration of the neutrophil to the site of tissue injury is governed, in part, by platelet endothelial cell adhesion molecule 1 (PECAM-1), CD99, and other adhesion molecules. These molecules are expressed on the surface of blood vessels and maintain the vascular permeability barrier. Evidence suggests that an antibody to PECAM-1 inhibits neutrophil transmigration and endotoxin-induced leukocyte sequestration in the lung, liver, and muscle. Neutrophil egress requires a chemotactic gradient through the extracellular matrix. Important chemotactic peptides include monocyte chemotactic protein 1 (MCP-1), platelet-activating factor (PAF), leukotriene B_4, and interleukin 8. Only small amounts of chemotaxis are required for the neutrophil to become responsive. A cascade of intracellular signaling pathways is activated when the neutrophil binds to the endothelium. These events eventually lead to conformational changes in the cytoskeleton of the neutrophil and permit transendothelial egress and rapid movement along the chemotactic gradient.

The neutrophil's primary objective is to destroy the microorganism, which is achieved through phagocytosis followed by intracellular killing. Specific immunoglobulins, such as IgG, enhance the phagocytic activity of the neutrophil and stimulate complement activation. The fusion of the phagosome with the lysosome, which contains powerful antimicrobial agents, aids in the killing of the microbe.

Release of reactive oxygen intermediates, formed by the enzyme NADPH, is the principal oxygen-dependent mechanism involved in the killing of microbes in the lysosome. In the neutrophil, the respiratory burst catalyzes the reduction of molecular oxygen (O_2) to superoxide (O_2^-), which is subsequently converted to hydrogen peroxide (H_2O_2) by superoxide dismutase. Hydrogen peroxide can form a hydroxyl radical in the presence of iron or other metals and can also form hypochlorous acid (HOCl) in the presence of myeloperoxidase. HOCl is the chemical that accounts for the cytotoxicity of the neutrophil in the presence of nitrogen-containing compounds. Enzymes such as lysozyme, elastase, lactoferrin, cathepsin, and defensins within the phagolysosome act synergistically to promote microbial killing.

8.3.4 Monocytes–Macrophages

The monocyte–macrophage also plays an important role in the response to microbial infection. There are many similarities between the neutrophil and monocyte–macrophage complex. Both phagocytose and use lysosomes to kill the pathogen. Both produce reactive oxygen intermediates on stimulation by LPS and IFN-γ. The monocyte evolves from a precursor (promonocyte) in the bone marrow, which undergoes maturation by acquiring specific granules. The monocyte then migrates to various tissues and organs where it further differentiates into macrophages. Tissue macrophages are the principal effectors in the defense against intracellular pathogens. They can phagocytose and destroy many common bacteria, but with less efficiency than the neutrophil. Macrophages express adhesion molecules such

as L-selectin and β_1 and β_2 integrins. This distinction is important since macrophages can still migrate to the site of inflammation in patients with leukocyte adhesion deficiency (lack of β_2 integrin). An important difference between the neutrophil and the macrophage is that the macrophage, after engulfing the bacteria, can present the antigenic fragments to the T lymphocytes in the context of major histocompatibility complex (MHC) class II molecules. This enhances the release of inflammatory cytokines and the microbicidal activity of the macrophage.

Like neutrophils, macrophages produce reactive oxygen species; however, they also produce nitric oxide (NO), which has diverse biological properties. NO is the product of the conversion of arginine to citrulline by nitric oxide synthase (NOS). Three isoforms of NOS exist: neuronal NOS (NOS-1) and endothelial NOS (NOS-3) are expressed constitutively. Inducible NOS (NOS-2, or iNOS) found in the macrophage is activated in response to inflammatory mediators. NO is relatively innocuous but can react with reactive oxygen species to form cytotoxic molecules. For instance, peroxynitrite is an important reactive nitrogen intermediate that is formed by the reaction of NO with O_2^- in inflammatory lesions in vivo and is responsible for the cytopathic effects of NO. NO may also react with metalloproteins to form S-nitrosothiols. Sustained overproduction of these compounds may lead to cellular injury and multisystem organ dysfunction.

8.3.5 Lymphocytes

Lymphocytes and natural killer cells are the predominant effector cells against intracellular organisms. Lymphocytes originate from the bone marrow; however, some leave the bone marrow to undergo maturation in the thymus. Once mature, T lymphocytes migrate to peripheral lymphoid organs such as the spleen, lymph nodes, and the Peyer's patches in the intestine, where they establish residence. Other lymphocytes mature in the bone marrow and become B cells, which produce immunoglobulins. The main job of T lymphocytes is to regulate cell-mediated immunity against intracellular pathogens. This requires recognition of the inciting antigen by MHC class II proteins, cellular activation, clonal expansion, and targeted killing. The MHC proteins on cell surfaces govern antigen presentation. Macrophages, dendritic cells, and B-lymphocytes can act as antigen-presenting cells. These cells phagocytose the microbe and digest it into smaller fragments or peptides that are then bound to the MHC class II proteins and then presented to T helper cells. In addition, any cell that is infected can present microbial antigens on its cell surface using MHC class I molecules. $CD8^+$ cytotoxic T lymphocytes then target these cells and release serine proteases to induce apoptosis.

8.3.6 Immunoglobulins

Immunoglobulins, or antibodies, represent a class of proteins that are synthesized from mature B-lymphocytes or plasma cells. The primary role of antibodies is to prevent microbial attachment to, or invasion of, the host epithelium. There are five major classes of immunoglobulins: IgA, IgG, IgM, IgD, and IgE. The predominant immunoglobulins are IgG, IgM, and IgA.

IgM, with its short half-life of 5 days, initiates the first response to an infection in the bloodstream. The levels of IgM then start to decrease while the levels IgG begin to increase. IgG, which is directed against bacteria and viruses, constitutes 85% of serum immunoglobulins found in the intravascular and extravascular compartments. The biologic potency of this protein resides in its ability to opsonize bacteria by binding the antigen to the neutrophil, monocyte, or macrophage.

Mucosal immunity is governed by IgA, which is synthesized by plasma cells within lymphoid tissue adjacent to the epithelial surface. Once secreted, IgA binds pathogenic microbes and prevents their attachment to the epithelial surface.

8.3.7 Cytokines

Cytokines are glycoproteins that orchestrate the interactions of immune cells with bacteria. Most of the immune cells secrete these proteins in response to an inflammatory or antigenic stimulus. The proinflammatory cytokines include TNF-α, IL-1, IL-6, IL-8, IL-11, IL-17, and IL-18. The earliest inflammatory cytokine to arrive at the site of injury is TNF-α. The principal anti-inflammatory cytokines are IL-10, IL-27, IL-33, and transforming growth factor-β (TGF-β), which help neutralize or modulate the production of inflammatory products from monocytes–macrophages. Recent data suggest that IL-17, IL-27, and IL-33 may play a novel and synergistic role in immune dysfunction and host response to sepsis and may be reasonable biomarkers for sepsis.

8.4 Neonates

In the United States, approximately half of the cases of sepsis in the pediatric population occur in neonates, specifically those born at low birthweights. Death or serious disability occurs in 40% of neonates with sepsis, versus a 10–20% mortality rate in older children. Neonates are predisposed to bacterial infections secondary to an immature cellular and humoral (antibody-mediated) immune system. The pool of neutrophils in the neonate represents only 20–30% of the total adult pool and consists of 60% circulating leukocytes and 15% immature bands. Neonates also have a limited ability to increase the pool of circulating neutrophils in response to infections. This predisposes the neonate to severe neutropenia because it takes at least 5–7 days to increase the formation of myeloid progenitor stem cells (precursors of neutrophils) in response to infections. Neutrophils in the neonate also demonstrate decreased adhesion to activated endothelium, less efficient phagocytosis secondary to deficiency in opsonins, and decreased ability to kill phagocytosed microbes by oxygen-dependent mechanisms.

T-cell-mediated immunity is also different in the neonate compared to older children and adults. There is a decrease in T-cell-mediated cytotoxicity due to the lack of prior antigenic exposure and a deficiency in cytokine production. Immunoglobulin M is more abundant in neonatal secretions, and the differentiation of B cells into IgA- or IgG-producing plasma cells does not occur for months after birth. The term neonate relies on the maternal transfer of IgG across the placenta during the third trimester and on the mother's breast milk, which is rich in IgG and IgA. By the fourth month of life, the neonate begins to increase production of IgG and the maternal IgG dissipates. As a result, neonates exhibit increased susceptibility to infections during the first four months of life.

In addition to a deficiency in cell-mediated and humoral immunity, the neonate is also at risk for infection due to immaturity of the antibody-independent complement system. The levels of key components of the complement system are decreased, which leads to a diminished capacity to fight off Gram-negative microbes (C9), decreased production of chemotactic factor C5a, and a decrease in functional opsonins due to a lack of efficient cross-linking (C3b).

8.5 Clinical Features and Diagnosis

The clinical presentation of sepsis in children and neonates may be subtle, and the diagnosis is nuanced in this population. While in the adult population, defining sepsis has moved toward clinical models for end-organ dysfunction (e.g., SOFA), according to the 2005 International Consensus Conference on Pediatric Sepsis, pediatric sepsis is still defined based on the presence of modified SIRS criteria. These criteria consider the specific physiologic changes that occur as children age and incorporate guidelines based on six age groups: newborns (0–7 days), neonates (7 days–1 month), infants (1–12 months), toddlers (2–5 years), children (6–12 years), and adolescents (12–18 years). Infection may be a diagnosis of pediatric sepsis that requires presence or suspicion of an infection, secondary to viral, bacterial, fungal, or rickettsial pathogens, and at least two of the following criteria:

1. Fever (core temperature > 38.5 °C) or hypothermia (<36 °C).
2. Tachycardia (heart rate [HR] > 2 standard deviations above normal for age OR bradycardia (HR < tenth percentile for age) in patients 1 year or greater.
3. Tachypnea (mean respiratory rate [RR] > 2 standard deviations above normal for age) OR mechanical ventilation (MV) for an acute process unrelated to neuromuscular disease or general anesthesia.
4. Leukocytosis or leukopenia OR 10% immature neutrophils.

Severe sepsis is defined as sepsis with cardiovascular dysfunction, acute respiratory failure, or dysfunction in two or more other organs. Septic shock occurs when the cardiovascular dysfunction is nonresponsive to isotonic fluid administration in the first hour. Notably, this patient population often maintains normotension despite progressive or worsening sepsis and thus hypotension is not required for the diagnosis of septic shock in children and neonates. Alternatively, tachycardia and signs of hypoperfusion, including increased capillary refill >2 seconds, altered mental status, decreased peripheral pulses, and decreased urine output, are more often diagnostic of shock in this population.

There are several significant changes that occur in the baseline physiology and response to injury or infection as children age. The modified SIRS criteria incorporate these changes and help guide the physician in diagnosis. For example, the diagnosis of pediatric SIRS requires the presence of either fever or leukocytosis but not both. Less than 50% of neonates with white blood cell counts greater than 20,000/mm^3 or less than 4000/mm^3 are ultimately diagnosed with an infection, and the presence of fever or hypothermia may be a more sensitive finding. In addition to the criteria listed above, the ratio of immature to total neutrophils may be useful in determining the likelihood of infection in the neonate. A ratio greater than 0.2 is a sensitive indicator of infection. Thrombocytopenia is a nonspecific and late predictor of neonatal sepsis, but trends in platelet count are important for the clinician to address. Similarly, children may maintain normotension until they have progressed to significant cardiovascular collapse. Thus, the modified SIRS criteria allow for the diagnosis of SIRS, sepsis, and shock in the presence of normotension. In the neonatal population specifically, hypoxemia, pulmonary hypertension, and cardiac collapse secondary to increased pulmonary vascular resistance during the transition from fetal to neonatal circulation further complicate the diagnosis and management of sepsis.

The most prominent clinical or physiologic change that occurs in SIRS, sepsis, and shock is reduced systemic vascular resistance (SVR), resulting in decreased peripheral extraction of oxygen. In response to this so-called "warm shock," the pediatric patient must increase cardiac output and increase minute ventilation to achieve a higher delivery of oxygen to ischemic tissues. An inadequate increase in oxygen delivery causes marked anaerobic metabolism and production of excess lactate. Increased lactate on hospital admission has been associated with increased risk for ICU admission, end-organ dysfunction, and mortality.

Notably, up to 50% of pediatric patients present with increased SVR or "cold shock," a phenomenon that is not observed in the adult population. A higher resting heart rate may lead to inadequate diastolic filling and resultant decreased cardiac output (CO). To compensate, children will initially have an increase in peripheral vasoconstriction, and hypotension will not occur until much later in the clinical course. Similarly, production of excess lactate may also be a rather late sign of sepsis and indicate a worse prognosis in children.

The 2001 International Sepsis Definitions Conference proposed a purely biochemical or immunological, rather than clinical, criteria to identify the inflammatory response in children. C-reactive protein (CRP), interleukin 6 (IL-6), and procalcitonin (PCT) were mentioned as potential markers for use in neonates and pediatric patients. PCT is secreted during Gram-negative sepsis from an unknown extrathyroidal source and may be used as a guide for antibiotic therapy. Maja Pavcnik-Arnol et al. performed a

prospective observational study investigating potential biochemical markers that could diagnose bacterial sepsis in the neonate. In critically ill neonates less than 48 hours old, LBP was a better marker of sepsis on the first day of suspected infection than IL-6 and PCT. In critically ill neonates older than 48 hours and older children, LBP was a better marker than IL-6 and CRP. In culture-confirmed sepsis, LBP had 91% sensitivity, 98% negative predictive value, 85% specificity, and 52% positive predictive value.

When there is suspected infection, cultures should be obtained from peripheral blood as well as any indwelling intravenous lines. Peripheral cultures should be obtained from at least two different venipuncture sites if possible. Once bloodstream infection is identified, repeat or follow-up cultures are not necessary in most cases. Subsequent blood cultures may be justified in patients who deteriorate clinically or who fail to improve despite appropriate antibiotic therapy. In some cases, bacteremia may be prolonged, necessitating further blood cultures during treatment. Urine cultures as well as lumbar puncture should be performed during the initial workup.

8.6 Management

Pediatric sepsis and septic shock management follow closely the guidelines of Pediatric Advanced Life Support (PALS). Upon recognition of end-organ dysfunction, the physician should initiate high flow O_2 support and establish intravenous or intraosseous access. The most prominent feature of pediatric SIRS, sepsis, and potential progression to septic shock is the increase in oxygen demand by end organs and a decrease in peripheral vascular resistance, which is manifested as a low blood pressure. In the treatment of sepsis, the goal is to increase oxygen delivery via aggressive fluid resuscitation, cardiovascular and respiratory support, and optimizing electrolytes, as well as hematologic, renal, metabolic, and nutritional needs. Initial resuscitation should include boluses of 20 mL/kg of isotonic saline up to 60 mL/kg in the first hour. Fluid boluses are continued until perfusion is improved. The physician should monitor for hepatomegaly, rales or crackles on auscultation, or other signs of volume overload during resuscitation. Fluid resuscitation of more than 40 mL/kg in the first hour following emergency department presentation is associated with improved survival and decreased occurrence of persistent hypovolemia and does not increase the risk of cardiogenic pulmonary edema. Delay in resuscitation as little as 30 min is associated with increased mortality in children over 2 years old.

If there is persistent hypoperfusion after isotonic fluid resuscitation, vasopressors should be initiated. The goal of vasopressor support is to maintain cardiac index between 3.3 and 6 L/min/m^2 and SVC oxygen saturation at 70%. Dopamine, dobutamine, and epinephrine are options for first-line vasopressor support. A 2015 double-blind, prospective randomized control trial demonstrated increased mortality risk with the use of dopamine when compared to epinephrine. Norepinephrine is used specifically in the presence of "warm shock" or hypotension with decreased SVR. Hydrocortisone administration can be considered in patients with vasoactive-resistant shock; however, prospective data are limited on this therapy.

Fluid resuscitation should continue, and the physician should monitor the urine output as a guide to end-organ perfusion and adjust fluid management accordingly (goal UOP 1–2 ml/kg/h). In addition, the use of mechanical ventilation may help relieve failing respiratory muscles. Adjustment to the respiratory rate or to the oxygen concentration on the ventilator is governed by arterial blood gas.

Source control with antimicrobial therapy is the cornerstone of the treatment of presumed sepsis or SIRS. Broad-spectrum antibiotics should be started within 1 hour of the first signs of sepsis, and source control should occur rapidly thereafter. Empiric antibiotic therapy should include coverage of both Gram-negative and Gram-positive organisms. Most children with sepsis or SIRS are diagnosed with Gram-negative bacterial infections from *E. coli*, *P. aeruginosa*, *Klebsiella*, and *Bacteroides* species. In neonates or term infants, the most common organisms

encountered are group B streptococcus, *E. coli*, and *L. monocytogenes*. Although culture is not required for the diagnosis of SIRS, sepsis, or septic shock, antibiotics should be tailored based on available culture data, and consultation with expert pediatric infectious disease specialists may be indicated to guide narrowing therapy or for multidrug-resistant infections. Empiric antifungal therapy may be indicated in patients with persistent fever or leukocytosis despite empiric antibiotics and unknown sources.

During systemic Gram-negative and Gram-positive bacterial infections, activation of the coagulation cascade is mediated by the extrinsic tissue factor pathway. Activated protein C is an endogenous regulator of coagulation and inflammation and is a promising therapeutic target in patients with severe sepsis. The PROWESS (Protein C Worldwide Evaluation in Severe Sepsis) study was a large multicenter randomized, double-blind, placebo-controlled trial in adult patients with severe sepsis. The trial demonstrated a decrease in the 28-day mortality from all causes in adults with sepsis treated with recombinant human activated protein C. Additional prospective studies are needed to determine if activated protein C is a viable option in the pediatric population.

Sepsis and SIRS cause a release of inflammatory cytokines and hormones that lead to hyperglycemia. Increased peripheral insulin resistance is caused by a release of cortisol, TNF-α, and IL-1. In addition, there is an increase in hepatic glucose production, which causes hyperglycemia. Van den Berghe and colleagues demonstrated that tight glycemic control with a blood glucose level of 80–110 mg/dl decreases in-hospital mortality by 34% in a mixed medical-surgical ICU (predominantly adult cardiac surgery patients) compared to patients with a targeted blood glucose level of 180–200 mg/dl. In septic neonates and children, hyperglycemia correlates with prolonged ventilator dependency and increased hospital length of stay.

Nutritional support during sepsis is paramount. The advantages of enteral feeds when compared to parenteral nutrition include buffering gastric pH, avoiding the use of centrally placed catheters, preserving of gut mucosa, limiting the introduction of bacteria and toxins from the gastrointestinal tract into the circulation, and preserving a more physiologic pattern of enteric hormone secretion.

Transfer to a pediatric tertiary care center should be initiated for any pediatric patient requiring vasoactive support. However, initial resuscitation should not be delayed to accommodate transfer.

8.7 Outcomes

Overall mortality from sepsis has decreased significantly in the pediatric population in the past 40 years, with currently reported mortality ranging from 10% to 20%. However, sepsis remains the leading cause of death in children worldwide, and the incidence continues to increase due to better diagnostic tools and understanding. Outcomes are impacted by time to resuscitation and clinical characteristics at the time of presentation. For every hour without adequate resuscitation, mortality increases by 40%. Goal-directed fluid resuscitation and vasoactive support in the first 72 hours reduce overall mortality. Furthermore, if hypotension is adequately reversed in the emergency room, mortality is reduced twofold.

8.8 Conclusion

Despite advances in the diagnosis and management of sepsis, it remains a major cause of death in children worldwide. Most commonly observed secondary to bacterial infection, the development of sepsis is influenced by the host defense and immune system as well as virulence of the pathogen. In children, sepsis is diagnosed based on a modified SIRS criteria, which includes fever or leukocytosis with tachycardia or tachypnea. Management of sepsis follows PALS guidelines for resuscitation and prioritizes delivery of oxygen therapy as well as fluid resuscitation and

early administration of broad-spectrum antibiotics. Outcomes in children with sepsis are impacted greatly by time to appropriate fluid resuscitation and antibiotic administration, and overall mortality ranges from 10% to 20% in this population.

Reference

Alaedeen DI, Walsh MC, Chwals WJ (2006) Total parenteral nutrition-associated hyperglycemia correlates with prolonged mechanical ventilation and hospital stay in septic infants. J Pediatr Surg 41(1):239–244, discussion 239–244

Further Reading

Adelman MW, Woodworth MH, Langelier C et al (2020) The gut microbiome's role in the development, maintenance, and outcomes of sepsis. Crit Care 24(1):278. (In eng). https://doi.org/10.1186/s13054-020-02989-1

Bernard GR, Vincent JL, Laterre PF et al (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344(10):699–709. (In eng). https://doi.org/10.1056/NEJM200103083441001

Brown KA, Brain SD, Pearson JD, Edgeworth JD, Lewis SM, Treacher DF (2006) Neutrophils in development of multiple organ failure in sepsis. Lancet 368(9530):157–169

Dahmer MK, Randolph A, Vitali S, Quasney MW (2005) Genetic polymorphisms in sepsis. Pediatr Crit Care Med 6(3 Suppl):S61–S73

Emr BM, Alcamo AM, Carcillo JA, Aneja RK, Mollen KP (2018) Pediatric sepsis update: how are children different? Surg Infect 19(2):176–183. (In eng). https://doi.org/10.1089/sur.2017.316

Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS (2013) Trends in the epidemiology of pediatric severe sepsis*. Pediatr Crit Care Med 14(7):686–693. (In eng). https://doi.org/10.1097/PCC.0b013e3182917fad

Leclerc F, Duhamel A, Deken V, Grandbastien B, Leteurtre S, (GFRUP) GFdReUP (2017) Can the pediatric logistic organ dysfunction-2 score on day 1 be used in clinical criteria for sepsis in children? Pediatr Crit Care Med 18(8):758–763. (In eng). https://doi.org/10.1097/PCC.0000000000001182

Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348(16):1546–1554

Morrow KN, Coopersmith CM, Ford ML (2019) IL-17, IL-27, and IL-33: a novel axis linked to immunological dysfunction during sepsis. Front Immunol 10:1982. (In eng). https://doi.org/10.3389/fimmu.2019.01982

Pavcnik-Arnol M, Hojker S, Derganc M (2004) Lipopolysaccharide-binding protein in critically ill neonates and children with suspected infection: comparison with pro-calcitonin, interleukin-6, and C-reactive protein. Intensive Care Med 30(7):1454–1460

Seymour CW, Liu VX, Iwashyna TJ et al (2016) Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315(8):762–774. (In eng). https://doi.org/10.1001/jama.2016.0288

Ventura AM, Shieh HH, Bousso A, et al (2015) Double-blind prospective randomized controlled trial of dopamine versus epinephrine as first-line vasoactive drugs in pediatric septic shock. Crit Care Med 43(11):2292–2302. (In eng). https://doi.org/10.1097/CCM.0000000000001260

Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC (2003) The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med 167(5):695–701