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Sepsis in Children

Selim Öncel

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Abstract

Sepsis is systemic inflammatory response syndrome due to a documented or suspected infection. Causative agents of sepsis include group B streptococcus, *Escherichia coli*, and *Listeria monocytogenes* in infants younger than 2 months, and community-acquired organisms. Bacteremia may ensue in patients whose defense mechanisms have become vulnerable due to many factors. Sepsis and septic shock can be viewed as clinical pictures, which develop as consequences of proinflammatory processes/cytokines leading to a state that cannot be restrained by anti-inflammatory processes/cytokines. As yet, a cytokine, which is uniquely associated with severe sepsis and septic shock and can be used as a biomarker, has not been discovered. Sepsis is a cytokine storm, which may adversely affect almost any organ system. Whether there is an association between the severity of sepsis or septic shock and cytokine gene polymorphisms is an important field of study. Mottled skin and prolongation of capillary refill time may help the physician recognize septic shock before hypotension emerges. The management of severe sepsis and septic shock involves (1) the hemodynamic support, (2) inotropes, vasopressors, and vasodilators, (3) antimicrobial therapy, (4) transfusions, and (5) corticosteroids as indicated. Hospital mortality of pediatric sepsis is 2–10%.

Keywords: sepsis, pediatrics, cytokines, sepsis-associated encephalopathy, systemic inflammatory response syndrome, neonatal sepsis

1. Introduction

Although sepsis can affect any individual at any time during her/his lifetime, it is more apt to occur and be destructive at the extremes of life, the very old and the very young.

It is sometimes referred to as “blood poisoning” in anglophone countries and in various manners elsewhere (e.g., “microbe in blood” in Turkey). The sepsis is the body’s deadly response to infection. Once sets in, sepsis can progress to septic shock and death if left untreated. One-third of people who develop sepsis die worldwide. These deaths occur more frequently in economically developing countries [1].

This chapter deals with pediatric sepsis with much greater emphasis on beyond neonatal period.

2. Definitions

Systemic inflammatory response syndrome (SIRS) is defined as two or more of the following items, one of which has to be the one marked with an asterisk (*) [2]:

1. Body core temperature of higher than 38.5°C or lower than 36°C*.
2. Except leukopenia caused by chemotherapy, a leukocyte count exceeding or lower than normal limit for age or immature leukocyte count above 10% of total leukocyte count*.
3. Abnormal heart rate:
 - (a) In children 1 year of age and over
 - Average heart rate in excess of two standard deviations from the age normal in the absence of external stimuli, long-term drug use, or painful stimuli
 - Persistent elevation in heart rate in 24 h without any other explanation
 - (b) In children less than 1 year of age
 - Average heart rate below 10th percentile for age in the absence of external vagal stimulus, beta-blocker, or congenital heart disease
 - Persistent depression in heart rate in half an hour without any other explanation
4. Average respiratory rate of more than two standard deviations above normal for mechanical ventilation that is being carried out for an acute process irrelevant of general anesthesia or an underlying neuromuscular disease.

Sepsis is SIRS due to a documented or suspected infection [2–5].

Organ dysfunction definitions are explained below:

1. If at least one of the following items is present despite isotonic intravenous fluid bolus (≥ 40 mL/kg in 1 h), this is called **cardiovascular dysfunction** [2]:
 - (a) Criteria for drop in blood pressure:

- Blood pressure is below fifth percentile for age OR.
 - Systolic blood pressure below two standard deviations of normal for age.
- (b) Vasoactive drugs required for maintaining normal blood pressure (5 $\mu\text{g/kg/min}$ dopamine or dobutamine of any dosage, epinephrine, or norepinephrine).
- (c) Presence of more than two of the following items:
- Unexplained metabolic acidosis with a base deficit of more than 5 mmol/L.
 - Arterial lactate concentration of more than two times the upper limit.
 - Urine output of less than 0.5 mL/kg/h.
 - Capillary refill time of more than 5 s.
 - The difference between core and peripheral temperature of more than 3°C.
2. If at least one of the following items is present, this is called **respiratory dysfunction** [2]:
- (a) Arterial oxygen partial pressure (PaO_2)/inspired oxygen fraction (FiO_2) ratio of less than 300 in the absence of pulmonary disease or cyanotic heart disease.
- (b) Initial measurement of arterial carbon dioxide partial pressure (PaCO_2) above 65 Torr or 20 mmHg.
- (c) Proven requirement for maintaining the saturation at or above 92% or FiO_2 of more than 50%.
- (d) Nonelective invasive or noninvasive mechanical ventilation requirement.
3. If at least one of the following items is present, this is called **neurological dysfunction** [2]:
- (a) Glasgow Coma Score of 11 or less.
- (b) Acute change in mental status together with a drop of Glasgow Coma Score of three or more points from abnormal baseline value.
4. If at least one of the following items is present, the situation is called **hematological dysfunction** [2]:
- (a) International normalized ratio (INR) above 2.
- (b) Platelet count below 80,000/ μL or has decreased 50% from the highest value recorded in the last 3 days (for chronic hematology-oncology patients).
5. **Renal dysfunction** is serum creatinine concentration of two times the upper limit for normal or more or twofold increase in baseline serum creatinine [2].

6. The presence of at least two of the following items is called **liver dysfunction** [2]:

- (a) Alanine transaminase (ALT) concentration of two times the upper limit for age.
- (b) Total bilirubin concentration of 4 mg/dL or more (not applicable for newborns).

For establishing the diagnosis of **acute respiratory distress syndrome (ARDS)**, the following criteria should be met [2]:

- $\text{PaO}_2/\text{FiO}_2$ ratio <200 mmHg.
- Bilateral infiltrates on chest X-ray.
- Acute onset.
- No sign of left heart failure present.

If, in addition to sepsis, there is cardiovascular organ dysfunction, ARDS, or two or more other organ dysfunctions, this situation is called **severe sepsis** [2].

3. Causative agents

Sepsis may be a consequence of infections due to bacteria, viruses, fungi, or parasites. Causative agents of sepsis include group B streptococcus, *Escherichia coli*, *Listeria monocytogenes* in infants younger than 2 months of age, and community-acquired organisms like *S. pneumoniae* and *Neisseria meningitidis* in children of 1–2 years. In a Canadian study of 6-year duration, the most common pathogens in bloodstream infections of childhood were *S. pneumoniae*, *Staphylococcus aureus*, and *E. coli* [6].

4. Pathophysiology

The site of infection, as the cause of sepsis, varies according to age. In infants, it is usually primary bacteremia. There is respiratory tract infection in nearly half of older children with sepsis [7].

Since sepsis is defined as SIRS, or in other words, pathological changes in body temperature, heart, or respiratory rates, and leukocyte count in the presence of proven or suspected infection, it would be prudent that we review the pathogeneses of the components of SIRS and infection that form sepsis and changes due to organ dysfunction in severe sepsis separately [2, 8].

4.1. Formation of infection

One of the most important clinical situations causing sepsis and septic shock is bacteremia. Bacteria must pass through the dermal or mucosal barrier in order that bacteremia takes place.

The pathogenesis of bacteremia is closely associated with the self-defense of the host and the characteristics of the bacteria. Organisms like *S. pneumoniae*, *N. meningitidis* and *Haemophilus influenzae* type b, which form a part of nasopharyngeal flora, cause bacteremia by overcoming mucosal defense systems with the aid of facilitating factors like upper respiratory infections. *N. meningitidis* is taken into the cylindrical epithelial cell with phagocytosis. After traversing the cytoplasm in the phagosome, it passes into subepithelial tissues. *H. influenzae* type b passes into subepithelial tissues by clinging to the epithelial cell and loosing the intercellular tight junctions making its way toward pharyngeal capillaries. *S. pneumoniae* attaches to specific receptors by means of which it enters the cell. The number of platelet-activating factor receptors located on surfaces of respiratory epithelial cells increases during viral infections. These receptors serve as attachment sites for pneumococci. Gram-negative organisms that are a part of gut flora also attach to specific receptors. Pili and adhesins on the microorganism surface play a pivotal role in this attachment. Pili were also shown to be important in the pathogenesis of sepsis caused by *Streptococcus pyogenes*, Group B streptococcus, and *S. pneumoniae* [9].

Bacteremia may ensue in patients whose defense mechanisms have become vulnerable due to many factors. The examples are as follows:

- With the intubation of an intensive care patient, protease activity increases whereas cell-bound fibronectin diminishes rendering cell surface receptors “sheathless,” which make them ideal binding sites for predominantly Gram-negative bacteria of gut flora [9].
- Viridans streptococci, elements of oral flora, may cause bacteremia in neutropenic children who have severe oral mucositis and receiving antineoplastic chemotherapy.
- Gram-negative gut bacteria cause bacteremia by traversing the gut mucosa (translocation), whose integrity has been disrupted by antineoplastic drugs.
- Staphylococci, thanks to their ability to adhere to hard surfaces, cause catheter-related bacteremia by colonizing in catheter lumina.

4.2. The process of cytokine synthesis

The word “cytokine” is made up of two Greek words, “cyto-” (cell) and kinos (movement). The cytokine concept was introduced to scientific world by Barry Bloom and John David, who, being unaware of each other’s similar research, discovered a cytokine, known as macrophage migration inhibitor factor today. Although cytokines were once classified as lymphokines, interleukins, and chemokines, according to their functions, and target and release sites, such a classification is avoided due to the abundance and substitution characteristics of cytokines [10].

Every cytokine has a corresponding cell surface receptor, with the stimulation of which begin signaling cascades, as a consequence of which some genes are upregulated or downregulated. In the end, either other cytokines or cell receptors for various molecules are synthesized, or the rate of synthesis of these substances decreases [10].

Sepsis and septic shock can be viewed as clinical pictures, which develop as consequences of pro-inflammatory processes/cytokines leading to a state that cannot be restrained by anti-inflammatory

processes/cytokines (**Table 1**). The human body responds in a pathological manner to infection, which is a pathological situation itself. The occurrence of sepsis or immune compromise depends on whether systemic inflammatory response or its opposite end, compensatory anti-inflammatory response syndrome, predominates the inner environment as a response to infection. Compensatory anti-inflammatory response syndrome is a clinical entity, which progresses primarily with T-helper depression due to catecholamine discharge and apoptosis of splenic B-lymphocytes [11].

When the causative organism enters the body, nonspecific (innate) immune system is stimulated. Mammals perceive the pathogen by means of pattern-recognition receptors, the most important and evolutionally the oldest of which are Toll-like receptors (TLRs), found in insects, plants, and mammals. TLRs are transmembrane proteins, so-called because of their similarity to a product protein of the gene Toll, which is named after the remark ("Das ist ja toll!" ("That's really cool!")) by Nobel Prize in Physiology or Medicine winner (1995) Christina Nüsslein-Volhard, who has reportedly shouted out as so in surprise when she realized a *Drosophila melanogaster* (common fruit fly) had assumed an amazing appearance as a result of

| Proinflammatory | Anti-inflammatory |
|---|---|
| TNF- α | IL-1Ra |
| IL1b, IL-2, IL-6, IL-8, IL-15 | IL-4 |
| Neutrophil elastase | IL-10 |
| IFN- γ | IL-13 |
| Thromboxane | Type II IL-1 receptor |
| Platelet-activating factor | Transforming growth factor-b |
| Vasoactive neuropeptides | Adrenaline |
| Phospholipase A ₂ | Soluble TNF- α receptors |
| Plasminogen activator inhibitor-1 | Leukotriene B ₄ -receptor antagonist |
| Prostaglandins | |
| Prostacyclin | |
| Free radicals | |
| Soluble adhesion molecules | |
| Tyrosine kinase | |
| Protein kinase | |
| H ₂ S | |
| NO | |
| High mobility group box 1 protein | |
| TNF: tumor necrosis factor, IL: interleukin, IFN: interferon. | |

Table 1. Major proinflammatory and anti-inflammatory mediators [12].

polymorphism of one of its proteins [13]. Transmembrane proteins have their extracellular, transmembrane, and intracellular parts. Humans have at least 10 different TLRs [14]. TLRs are found in abundance on leukocytes, macrophages, and some kinds of endothelial cells [11]. It is noteworthy that some TLRs are found on cytoplasmic membrane and some on the membrane of endocytic vesicles. These receptors recognize many organisms, from bacteria to fungi, and from protozoa to viruses. Although a part of nonspecific immune system, TLRs vary with respect to the patterns concerning the component of the organism they recognize. For instance, whereas TLR4 is unique in recognizing lipopolysaccharide of Gram-negative bacteria, mannan of *Candida albicans*, and glucuronoxylomannan of *Cryptococcus neoformans*, glycosylphosphatidylinositol moieties of *Plasmodium falciparum* are recognized by either TLR4 or TLR2. Hemozoin of *P. falciparum* is exclusively recognized by TLR9 [15].

Stimulated TLRs cause many protein kinases to be phosphorylated, in other words, become active. Reactions of these highly complex biochemical pathways take place in cytosol or endosome. Some of the biochemical pathways are dependent on a mediator molecule named MyD88, and some are not. For example, proinflammatory cytokines in sepsis and septic shock are released in a MyD88-dependent pathway. The end products of these pathways (nuclear factor kappa B (NF κ B), interferon regulatory factor 3 (IRF3)) traverse the nuclear membrane and induce related genes by adhering to promoter regions of deoxyribonucleic acid (DNA). NF κ B activity is inhibited by the most-studied heat-shock protein HSP70, which, thus, diminishes the inflammatory response. HSP70 reduces the damage caused by excessive inflammation by decreasing apoptosis and preserving cell proteins [16].

Significant information has been obtained with the study of inflammatory processes, especially those induced by Gram-negative bacteria. Septic shock occurs via similar mechanisms with Gram-positive organisms. Here, instead of lipopolysaccharide, which is found in abundance in Gram-negative organisms, less potent cell wall molecules, such as peptidoglycan and teichoic acid, cause similar inflammatory responses.

Gram-negative bacteria have a thin cell wall made up of a single layer of peptidoglycan, out of which there is a cell membrane consisting of lipopolysaccharide, which is a strong stimulator of immune response. The lipopolysaccharide molecule has three main components [17]:

1. **Lipid A** is responsible for the biological activity of endotoxin. Its structure is almost the same in different strains.
2. **Core polysaccharide** is made up of oligosaccharides, but its structure is highly diverse among species, even within strains.
3. **Oligosaccharide side chains** vary among strains. It consists of repeating units (e.g., 40 repetitions in O antigen) and is the moiety which provides the O antigen its antigenic specificity.

Lipopolysaccharide first binds to lipopolysaccharide-binding protein (LBP) in plasma. LBP-lipopolysaccharide complex binds to CD14 molecule on the plasma membrane. This new complex binds to TLR4/MD ("myeloid differentiating factor")-2, which is also on the plasma

membrane [18]. This structure, activating various protein kinases, as outlined above, causes cytokine release when the end products bind to promotor regions on DNA [19].

There are countless cytokines playing roles in sepsis and septic shock. These mediators, causing release of each other, create an enormous mediator cascade. The mediator cascade is initiated by the stimulation of tumor necrosis factor (TNF) (cachectin) production by stimulators like lipopolysaccharide, C5a, viruses, and enterotoxins. TNF appears to be the main cytokine initiating and playing a pivotal role in the progression of the mediator cascade. TNF, released from many cells, such as monocytes, macrophages, natural killer cells, microglial cells, and hepatic Kupfer cells, causes countless mediators (e.g., interleukin(IL)-1 β , IL-6, eicosanoids, platelet activation factor) to spill into blood in an uncontrolled manner resulting in a very severe inflammatory response and endothelial damage. However, there are many cytokines, the productions of which do not necessitate the presence of TNF [20]. As a consequence of this process, typical signs of endotoxic shock will show up. Some of the cytokines released (e.g., TNF- α , IL-1, and IL-6) cause free oxygen radical and protease release from other immune system cells, such as neutrophils, prostanoids leukotrienes, thromboxanes, nitric oxide, and endothelin from endothelial cells. Some of these substances are useful in killing bacteria but some (e.g., nitric oxide) are known to cause mitochondrial dysfunction by deactivating the catecholamines in the circulation. Mediators, whose release is induced by lipopolysaccharide, increase nitric oxide synthase II production and thus nitric oxide (endothelial-origin relaxation factor) production. Nitric oxide is a potent vasodilator and is the primary substance responsible for the hypotension in septic shock. Besides, nitric oxide causes vasodilation, which in turn causes diminished perfusion pressure in capillary network and blood flow by opening collateral channels. Decreased capillary flow results in organ hypoxia despite high blood flow because of vasodilation.

We have enough knowledge on how sepsis and septic shock develop, but it is surprising that only a few histopathologic changes concerning cell death are present in patients who have died of severe sepsis. Apart from cellular apoptosis in spleen and intestines, myopathic changes in skeletal muscle, and changes in vascular morphology in meningococcal sepsis, there is no serious sign of necrosis in main organs.

Then, studies have concentrated on microcirculation and mitochondrial dysfunction, and theories on how adenosine triphosphate (ATP) production can decrease under normal, even supranormal oxygen partial pressures, have been put forward. These theories include diminished pyruvate entry into tricarboxylic acid cycle, activation of poly-(ADP-ribose) polymerase, and uncoupling of oxidation from phosphorylation. Another cause of tissue hypoxia is nitric oxide's combining with free oxygen radicals (O_2^-) to form peroxynitrite ($ONOO^-$) resulting in reversible or irreversible binding of these three substances to proteins in the electron transport chain, such as succinate dehydrogenase and cytochrome c oxidase. As a result, ATP production decreases, being unable to meet the needs of the energy-consuming cell, and cell death takes place. This process accounts for the unexpectedly few histopathologic changes in autopsies. Complement system is activated through contact with bacterial molecules or binding of proteins, such as antibody or mannose-binding lectin, to these molecules. Complements like C3b and C5a cause migration of leukocytes and increase inflammation [11].

The balance between thrombogenesis and thrombolysis has been disrupted in sepsis. There is endothelial damage due to direct effect of microorganisms, cytokines, and fibrin deposition triggered by endothelial dysfunction. As a result of this, a process of simultaneous thromboses and bleedings, which is known as consumption coagulopathy or disseminated intravascular coagulation (DIC), develops. DIC is more frequently encountered in Gram-negative sepsis (e.g., meningococcal sepsis) than in Gram-positive sepsis. The most common complications of DIC are thromboses of great vessels, liver infarction, acute renal failure, cerebral hemorrhage, and cerebral infarction [21].

4.3. Cytokines as sepsis biomarkers

TNF, IL-1b, and IL-6 are the first cytokines to regulate the initial response of the innate immune system. TNF and IL-1b activate endothelial cells and attract the granulocytes in circulation to inflammation site. TNF and IL-1b cause fever and other systemic signs by entering the circulation. IL-6 increases the production of what is known as acute phase proteins (e.g., C-reactive protein) in liver and more granulocytes in bone marrow. As can easily be seen, TNF, IL-1b, and IL-6 are responsible for the formation of SIRS and could be thought of being used as sepsis biomarkers [22].

TNF and IL-1b concentrations increase in endotoxin-associated Gram-negative sepsis. TNF or IL-1b administration to laboratory animals is as effective in the formation of septic shock as the endotoxin itself, but in clinical studies, TNF and IL-1b could not be used as sepsis biomarkers because

- TNF concentrations before anti-TNF antibody treatment do not affect the outcome.
- IL-1b does not rise as TNF does.

Of the three cytokines mentioned above, IL-6 has attracted the most attention. The causes of this include

- The role of IL-1b, IL-1a, and the receptor antagonist of IL-1 in the development of sepsis is debated [22].
- The relatively higher reliability of measurement of the plasma concentration of IL-6.
- The usability of IL-6 in the diagnosis and treatment of autoimmune rheumatologic diseases.
- The availability of commercial immunoassay kits, contrary to TNF and IL-1b.

Nevertheless exactly as in TNF and IL-1b, IL-6 is not specific to sepsis and its role as sepsis biomarker is prognostic, rather than diagnostic. In many studies, rise in IL-6 concentration is associated with higher mortality. This characteristic can be used to detect patients who may benefit from therapy [22].

Since the clinical signs of sepsis in neonates are very subtle and nonspecific, predictive biomarkers are needed, particularly in economically developing countries, where the incidence, morbidity, and mortality of early neonatal sepsis (ENS) (sepsis diagnosed less than 72 h after

birth) are particularly high. Evidence published to date is still far from convincing the physician to use procalcitonin as a biomarker for routine use in clinical practice as a risk stratifier and a prognostic predictor or even to guide the duration of antibiotic treatment and bedside decision making [23]. The results of a new study by He et al. indicate that elevated IL-27 strongly correlates with ENS and may provide additional diagnostic value along with procalcitonin [24].

The usage of IL-6 and LBP in pediatrics is also promising. In newborns with late sepsis risk, IL-6 rises 48 h before bacterial sepsis becomes clinically manifest [25]. Initial high IL-6 concentrations predict future septic shock in hospitalized children [26]. Initial high IL-6 concentrations foretell high risk of septic shock and mortality in pediatric burn patients [27]. LBP points to invasive bacterial infections and bacterial infections in children and newborns over 28 weeks of gestational age, respectively [28–30]. LBP can differentiate between SIRS and ENS in newborns within the first 48 h of their lives [30].

While homing chemokines serve to regulate adaptive immune system, especially in secondary lymphoid tissue, proinflammatory chemokines attract granulocytes and monocytes to the site of inflammation and promote their extravasation. Chemokines, thanks to these properties, can be used as biomarkers in sepsis, and some of them have been shown to be superior to IL-6 in that aspect. Examples are IL-8 (in the diagnosis of sepsis) and monocyte chemoattractant protein (MCP)-1 (in the determination of sepsis mortality) [31]. According to the results of a study, among 17 cytokines (IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, interferon- γ , granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, MCP-1, macrophage inflammatory protein-1, and TNF- α), the cytokines most closely associated with organ dysfunction within 24 h are IL-8 and MCP-1 [31]. As yet, a cytokine which is uniquely associated with severe sepsis and septic shock and can be used as a biomarker has not been discovered [32].

4.4. Effect of cytokine storm on tissues and organs

- Cardiovascular system

Myocardium is depressed in septic shock. The reason for this depression is not hypoperfusion, but depressing cytokines like TNF and IL-1 β in the circulation. Ventricles dilate and ejection fraction drops. As a result, hypoperfusion ensues in peripheral tissues. Peripheral hypoperfusion and hypoxia lead to overproduction of lactic acid, which is another myocardial depressor. This chain of events persists as a vicious cycle [21].

- Respiratory system

Alveoli are diffusely damaged because of circulating endotoxins. In the exudative phase of this damage, proteinaceous edema fluid accumulates in alveoli, and type I epithelial cells are injured. In this clinical picture, which is also known as shock lung, alveolar collapse, hemorrhage, edema, hyaline membrane formation, which is made up of fibrin and necrotic epithelial cells on epithelial surfaces of respiratory bronchioles and alveolar ducts, and neutrophil accumulation in alveolar capillaries occur. Unless treated,

severe pulmonary edema develops despite low central venous pressure, and as a result, ventilation-perfusion mismatch ensues. This clinical picture is called ARDS. In the regeneration phase, healing occurs via return to normal structure or pulmonary fibrosis. Lost type 1 cells are replaced by proliferating type 2 cells. Superimposing infections and barotrauma due to mechanical ventilation worsen respiratory system functions [21].

- Kidneys

Nitric oxide disrupts blood distribution in renal medulla and cortex. With the effect of nitric oxide and cytokines, renal tubule function, which requires high energy input, deteriorates due to decreasing ATP production. As a consequence of hypotension, increase in the release of endothelin, which is a vasopressor hormone, and activation of renin-angiotensin-aldosterone system pave the way to sodium and water retention, which makes a ground for renal failure. Neutrophil adhesion and microthrombi further diminish the glomerular filtration rate. The question of why renal failure in sepsis, despite anuria and despite its presence even in patients who die of sepsis, can develop without acute tubular necrosis and why it takes renal function so long (months) to return to normal while systemic inflammation has already disappeared and circulatory function has returned to normal still stands as an enigma and awaits to be elucidated [11, 21].

- Central and peripheral nervous system

The most important one among the effects of sepsis on central nervous system is sepsis-related encephalopathy and critical illness polyneuropathy. The causes of encephalopathy include disruption of blood-brain barrier, coagulopathy-related cerebral hemorrhage, microinfarctions, hypoxic-ischemic encephalopathy, metastatic brain abscesses, meningitis, and cytokine storm. While this clinical entity, which manifest itself with delirium and confusion, is often reversible, it may lead to self-mutilism of the patient in intensive care and development of cognitive and behavioral dysfunction in the long term.

The diagnosis of this clinical picture, which manifests itself also with flaccid paralysis and loss of deep tendon reflexes, is usually made only during or after separation of the patient from ventilator due to encephalopathy, administration of neuromuscular drugs, and the unfavorable general situation of the patient. Prognosis varies according to the severity of illness and patient's age. Muscle weakness may last for months [21].

- Gastrointestinal system

Gastrointestinal system is negatively affected by sepsis due to hypoperfusion. Gastrointestinal bleeding may ensue as a consequence of splanchnic hypoperfusion, increase in intestinal permeability, bacterial translocation, stress ulcers, and coagulopathy.

Although liver is relatively resistant to sepsis, transaminase elevation, peribiliary infarctions, and cholestatic jaundice may ensue as a result of hypotension [21].

- Immune system

Although an immunologic hyperreaction itself, sepsis further disrupts the integrity of the immune system. In survivors of sepsis, mortality rate is higher in the following several

years than that in normal population, which can be attributed to a vague immune disorder with cytokines and chemokines [21, 33]. Overproduction of anti-inflammatory cytokines may be a cause of immune deficiency in sepsis, but there is no evidence that the abundance of anti-inflammatory cytokines (such as IL-1 receptor antagonist and soluble TNF receptors) in the environment is sufficient for putting away the effects of proinflammatory cytokines [20].

- **Extremities**

A clinical picture of skin bleeding and necrosis due to microvascular thrombi and subsequent perivascular hemorrhage may develop, especially in the presence of disseminated intravascular coagulation. This is called purpura fulminans (PF). Although most frequently encountered in *N. meningitidis* bacteremia, PF may ensue in bloodstream infections due to *S. pneumoniae* and capsulated microorganisms of any kind. In addition to necroses in PF, vasoconstriction in sepsis may be severe enough to cause infarctions of fingers and autoamputation. Vasopressor drugs, if administered without fluid resuscitation, increase the risk for this complication [21, 33].

- **Mental status**

Psychological disorders, such as posttraumatic stress disorder (in 20% of ARDS patients), depression, panic attack, public isolation, inability to stay alone or in crowded areas, and decrease in sexual activity, are seen frequently in survivors of sepsis [21].

4.5. The role of gene polymorphisms in predisposition to sepsis

Whether there is an association between the severity of sepsis and septic shock and cytokine gene polymorphisms is an important field of study. Such a connection could not be shown with IL-1, IL-1 receptor antagonist, and IL-10 genes. It has been postulated that TNF2, being a rare TNF gene (adenine at -308 position), may be associated with high promoter activity, but no elevation in the prevalence of TNF2 allele in patients having frequent attacks of severe sepsis and infections due to Gram-negative organisms has been noted. There is a publication stating that rare Arg753Gln mutation of TLR2 renders individuals prone to staphylococcal sepsis [33]. Single-nucleotide polymorphism in IL-1 β gene was found associated with higher mortality [34].

5. Medical history

In sepsis, complaints leading to the child being brought to the physician vary according to the source of infection or SIRS. Fever, hypothermia tachypnea, stomach ache, vomiting, diarrhea, clouding of consciousness, or several of these may be present in the child. Features in the history such as the child's immunization status, past infections, and attending daycare should be taken into notice [35].

6. Physical examination

Fever or hypothermia (core body temperature $<36^{\circ}\text{C}$) may be observed [5]. Abnormalities in other vital signs may also be detected. Normal limits of vital signs according to age are depicted in **Table 2** [36].

Shock may not be present in sepsis. Hypotension is not a prerequisite for shock. Mottled skin and prolongation of capillary refill time may help the physician recognize septic shock before hypotension emerges [2, 5].

| Age group | Bradycardia (pulse/min) | Tachycardia (pulse/min) | Respiratory rate (respirations/min) | Systolic blood pressure (mmHg) |
|-------------------|-------------------------|-------------------------|-------------------------------------|--------------------------------|
| 0 day to 1 week | <100 | <180 | >50 | <65 |
| 1 week to 1 month | <100 | <180 | >40 | <75 |
| 1 month to 1 year | <90 | <180 | >34 | <100 |
| 2–5 years | <80 | <140 | >22 | <94 |
| 6–12 years | <70 | <130 | >18 | <105 |
| 13–18 years | <60 | <110 | >14 | <117 |

Table 2. Normal of vital signs according to age [36].

7. Laboratory tests

In a child suspected of having sepsis, the following tests may be ordered: complete blood count (always with differentials), a reasonable metabolic panel (electrolytes, glucose, liver function tests, and albumin), serum lactate, arterial blood gases, coagulation studies, amylase, lipase, urinalysis, sputum culture, and Gram stain [35]. Leukocytosis or leukopenia may be present in children with sepsis (**Table 3**) [2].

Antibiotics should be started after blood and other cultures being drawn unless a delay of longer than 45 min is expected because of this process. According to the results of a recent study, the diagnosis of pediatric septicemia through BACTEC 9240 is quicker with high yield and great sensitivity compared to the conventional technique [37]. Blood cultures are recommended to be taken from a peripheral vein and a catheter, which has been in place for more than 48 h into a set of aerobic and anaerobic bottles and as at least two sets. In case the volume of the blood is insufficient, the sensitivity of the blood culture will decrease, and vice versa [38, 39]. The author suggests that anaerobic blood cultures not be taken from children routinely, since

- The volume of blood that can be taken from children is limited.
- True anaerobic blood stream infections are rare ($<5\%$) in children.
- Instead of sets consisting of one aerobic and one anaerobic bottle, selective culture for anaerobic organisms with two aerobic bottles yields better results (6% more positives).

- Since sensitivity patterns of anaerobes are well known, they can be covered effectively with empirical therapy.

| Age group | Leukocyte count ($\times 10^3/\mu\text{L}$) |
|-------------------|---|
| 0–7 days | >34 |
| 1 week to 1 month | >19.5 or <5 |
| 1 month to 1 year | >17.5 or <5 |
| 2–5 years | >15.5 or <6 |
| 6–12 years | >13.5 or <4.5 |
| 12–18 years | >11 or <4.5 |

Table 3. Leukocyte counts according to age [2].

Even if anaerobic blood cultures are to be drawn, the indications should be limited to risky situations as below [40–42]:

- Children displaying abnormal abdominal symptoms and signs.
- Children with sacral decubitus ulcers or cellulitis.
- Patients with poor oral hygiene, severe oral mucositis, or chronic sinusitis.
- Neutropenic children receiving high-dose corticosteroid therapy, which may mask abdominal symptoms.
- Children with sickle cell disease.
- Infants of mothers with prolonged rupture of membranes or chorioamnionitis.
- Children thought to have bacteremia due to a human bite or crushing trauma.

When clinically indicated, cultures may be taken from urine, cerebrospinal fluid, wounds, respiratory secretions, and other body fluids. Most accurate results will probably be obtained with double quantitative blood cultures in case of an intravascular device-related bloodstream infection. Mannan, antimannan, and 1,3 beta-D-glucan tests may be used if invasive candidiasis is suspected. Imaging techniques are very useful to delineate the foci of infection and to decide whether the patient’s condition is suitable for transport [5].

8. Diagnosis and differential diagnosis

Risk-scoring systems may guide the physician in deciding the presence of a serious bacterial infection [43]. As mentioned above, if a probable or proven infection is present with SIRS, the child is in sepsis. Sepsis should be differentiated from other causes of SIRS (e.g., trauma, burn, acute pancreatitis, drug reaction (acetaminophen, cytarabine, IL-2)) and hypotension

(e.g., hypovolemic shock, cardiogenic shock, neurogenic shock, and adrenocortical insufficiency) [4, 44–46]. The value of procalcitonin and other biomarkers in the differential diagnosis of sepsis is under investigation [5].

9. Management

The management of severe sepsis and septic shock involves the following phases:

9.1. Hemodynamic support

Hemodynamic support should be started promptly without waiting for the intensive care admission. A protocol on recognizing septic shock in emergency ward may shorten the time that is passed for the initiation of appropriate therapy [47]. Although central venous line is preferred, fluids may be given through peripheral veins or via intraosseous route if a central venous catheter is not present or cannot be placed [5, 48]. Initial recommended fluid is crystalloid (e.g., normal saline) in boli of 20 mL/kg, each administered in 5–10 min. It should be kept in mind that mortality in children may be reduced if albumin is used in the initial fluid [49]. These crystalloids or colloid boli are continued until the perfusion returns to normal and the total given fluid volume reaches 60 mL/kg or more unless hepatomegaly or rales develop [48]. It is imperative that fluid resuscitation be given as rapidly as possible and not sparingly. The mortality in children who were given a total of more than 40 mL/kg is about 40% lower than those given a total of less than 20 mL/kg. The duration of intensive care and hospital stay become shorter (2–3 days) in patients given 60 mL/kg of fluid in the first 60 min than those who are not [50–52]. Inotropic support is recommended instead of fluid replacement if hepatomegaly or crackles are present. If the child has severe hemolytic anemia and blood pressure is normal, blood transfusion should be preferred to crystalloid or albumin boli [5].

For children in respiratory distress or hypoxia, oxygen should be administered with a mask; thereafter, if needed and if possible, high-flow oxygen through nasal cannula or nasopharyngeal continuous positive air pressure (CPAP) may be carried out [5, 48]. An adequate cardiovascular resuscitation reduces the likelihood of cardiovascular instability if mechanical ventilation is needed [5].

In the early management (in the first hour and in emergency ward), clinical goals for the septic shock patient are the following:

- Bring the capillary refill time back to 2 s or less.
- Provide blood pressure normal for age.
- Obtain a normal pulse and heart rate by removing the difference between central and peripheral pulses.
- Warm the extremities.
- Raise the urine output above 1 mL/kg/h.

- Restore hypoglycemia and hypocalcemia back to normal.
- Restore mental status.

Antibiotics should have been started meanwhile [5, 48, 53].

Goals to be realized by invasive monitorization of the patient are as follows:

- Central venous oxygen saturation of 70% or above and
- Cardiac index of 3.3–6 L/min/m² [5, 54]

9.2. Inotropes, vasopressors, and vasodilators

The patients whose initial fluid therapy has been completed in 10–15 min and who are unresponsive to this therapy (twice crystalloid or colloid boli) should have been started inotrope support at about 15th min of management through a peripheral vein if necessary until central venous route is assured [5, 55]. The goals at this stage of the management are as follows [5]:

- Normal perfusion pressure (mean arterial pressure, central venous pressure): 55 mmHg for term newborns, 60 mmHg for children 1 month to 1 year of age, 65 mmHg for children aged 1–15 years.
- Central venous oxygen saturation (ScvO₂) = 70%.
- Cardiac index = 3.3–6 L/min/m².

In cold shock with normal blood pressure but abnormal capillary refill time (>2 s), the dosage of dopamine given through central vein can be increased to 10 µg/kg/min. If shock is refractory to dopamine, epinephrine (0.05–3 µg/kg/min) should be given; ScvO₂ and hemoglobin (Hb) should be kept above 70% and 10 g/dL, respectively. If ScvO₂ persists below 70%, a vasodilator, such as milrinone and imrinone, should be added to therapy; levosimendan should be considered to be started [5, 48].

In cold shock with low blood pressure, ScvO₂ and Hb should be kept above 70% and 10 g/dL, respectively. If shock is refractory to dopamine, epinephrine (0.05–3 µg/kg/min) should be given; if hypotension persists, norepinephrine should be started. If ScvO₂ is still below 70%, dobutamine, milrinone, enoxsimone, or levosimendan should be considered [5, 48].

In warm shock with low blood pressure, the rate of norepinephrine should be adjusted such that ScvO₂ stays above 70%. If hypotension persists, vasopressin, terlipressin, or angiotensin should be considered. If ScvO₂ is still below 70%, low-dose epinephrine should be considered [5, 48].

In some patients, in whom systemic vascular resistance is very low despite norepinephrine administration, vasopressin, and terlipressin were used, but no benefit from these drugs has been shown in randomized studies [56–60]. In patients with low cardiac output, but high systemic vascular resistance, vasodilators such as

- Calcium sensitizer (levosimendan).
- Type III phosphodiesterase inhibitors (amrinone, enoximone, or milrinone).

- Nitrovasodilators.
- Prostacyclin.
- Fenoldopam.
- Pentoxifylline.

have been proposed in addition to inotropes [5].

If no response is taken with this therapy, the case is accepted as catecholamine-resistant shock, and the patient should be started hydrocortisone if at risk for absolute adrenal insufficiency [5, 48].

If catecholamine-resistant shock persists, pneumothorax, pericardial effusion, and high intraabdominal pressure should be excluded or corrected if present; pulmonary artery catheter, pulse contour cardiac output catheter, and femoral artery thermodilution catheter should be used or Doppler ultrasonography should be considered to receive some guidance on therapy [48].

If, despite all these measures, shock cannot be taken under control, extracorporeal membrane oxygenation (ECMO) should be considered [5, 61, 62].

9.3. Antimicrobial therapy

After severe sepsis is recognized, antibiotics should be started in the first hour, even in the first 15 min if possible. Cultures should be taken before initializing therapy if feasible, but therapy should not be delayed for this reason. The choice of antibiotic should be in accordance with endemic or epidemic data. Intramuscular or oral route may be used until intravenous access is made. In toxic shock syndromes with refractory hypotension, clindamycin and antitoxin are recommended. The management of *Clostridium difficile* colitis is preferentially carried out with enteral antibiotics; vancomycin should be used for severe colitis. Antimicrobial therapy should continually be reevaluated with regard to deescalation [5].

Combination empirical therapy is recommended for neutropenic patients with severe sepsis and in places where difficult-to-treat organisms, such as *Acinetobacter* and *Pseudomonas*, are prevalent. This therapy should be in the form of a wide-spectrum beta-lactam antibiotic + an aminoglycoside/quinolone in places where the risk of infection due to *Pseudomonas* is high. If the prevalence of *S. pneumoniae* is high, a beta-lactam + macrolide combination is recommended. Combination therapy should be of short duration (3–5 days or less) according to antibiotic-sensitivity results [5].

The duration of antimicrobial therapy should be limited to 7–10 days unless

- The response is slow,
- The infection focus is undrainable,
- *S. aureus* bacteremia is present,
- Some fungus or virus infections are present,

- An immunologic disorder with neutropenia is present, or
- Pneumonia due to *Pseudomonas spp.* or other Gram-negative rods is present [5, 63].

Narrowing the antimicrobial spectrum and shortening the duration of antimicrobial therapy would prevent superinfections due to other agents, such as *Candida spp.*, *C. difficile*, and vancomycin-resistant *Enterococcus faecium* [5].

Antiviral therapy should be started in sepsis or septic shock due to viruses. Antimicrobial therapy should be stopped in case that the cause of sepsis was detected as something other than infection. The removal of infected intravascular devices, especially central venous catheters, if possible and if preferred to antibiotic lock methods, will reduce mortality and increase the chances that the infection will be cured [5, 64].

9.4. Transfusions

If superior vena cava oxygen saturation is low (<70%), Hb concentration should be maintained at 10 g/dL. After hypoxemia and shock subside, the goal for Hb should be over 7 g/dL. Higher concentrations may be needed if acute bleeding, severe hypoxemia, or ischemic heart disease is present [5, 65, 66].

Platelet transfusion is indicated if the platelet count is

- Below 10,000/ μ L without a detectable bleeding.
- Below 20,000/ μ L if the patient has significant bleeding risk.
- Below 50,000/ μ L in the presence of active bleeding or in situations requiring either surgical or invasive procedures.

Plasma therapy should be brought to the agenda in case of thrombotic purpura situations, such as progressive disseminated intravascular coagulation due to sepsis, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura. In the absence of planned invasive intervention or bleeding, antithrombin therapy, erythropoietin administration for sepsis-associated anemia, and fresh-frozen plasma therapy should be avoided.

9.5. Corticosteroids

Hydrocortisone should be given to children with severe sepsis only in the presence of suspected or proven adrenal insufficiency, because there are publications both favoring (for reduction in mortality) and discouraging (for increasing mortality) its use [5, 67, 68]. Risk factors for adrenal insufficiency include severe septic shock with purpura, steroid use for chronic illness, and hypophysis or adrenal gland abnormalities. Hydrocortisone infusion is started with the dosage of 50 mg/m²/24, which may be needed to be increased up to 50 mg/kg/day in a short time. The measurement of baseline serum cortisol concentration may be useful at the onset of therapy [5].

9.6. Miscellaneous recommendations

In ARDS, tidal volumes exceeding 10 mL/kg should be avoided. Plateau pressure, arterial pH, and arterial partial oxygen pressure should be maintained at 30 cmH₂O or below, between 7.3–7.45 and 60–80 Torr (8–10.7 kPa), respectively. The Hb goal of 10 g/dL in unstable patients should be taken as 7 g/dL after recovery from shock and deep hypoxia [69].

Water retention in patients recovering from shock should be treated with diuretics. If this fails, continuous venovenous hemofiltration or intermittent dialysis should be carried out in order to prevent water retention of more than 10% of the body weight [5].

In children with septic shock, glucose concentration should be maintained below 180 mg/dL since concentrations of 178 mg/dL and over are associated with higher mortality. In newborns and children, insulin therapy should be given along with glucose infusion, the rate of which should be 4–6 mg/kg/min (6–8 mg/kg/min in newborns). The alternative is giving maintenance fluids prepared with 10% dextrose in water [5, 70].

Although no sedative or sedation protocol is recommended for patients with sepsis and mechanical ventilation support, long-term propofol should be avoided in children below 3 years for its association with fatal metabolic acidosis. Etomidate and dexmedetomidine should also be avoided due to its inhibitory effect on adrenal axis and sympathetic nervous system, the integrity of which is essential for hemodynamic stability in septic shock [5].

Enteral route should be preferred to parenteral route in nutrition. Glucose requirements of newborns and children can be met with sodium-containing fluids prepared with 10% dextrose in water and administered at maintenance rate.

10. Prognosis

Hospital mortality of pediatric sepsis is 2–10% [5]. In United States, hospital mortality in severe sepsis has declined from 10% in 1995 to 4% in 2003 [71, 72]; this is probably because septic shock is increasingly recognized more readily and earlier in the course and treated more aggressively [73].

Seven and six percent of children who are discharged from hospital after surviving postneonatal sepsis die within 28 days and afterward, respectively (early and late mortality). About half of those who survive these 28 days are rehospitalized at least once. Comorbidity is important in the development and late mortality of and rehospitalization in pediatric sepsis [74, 75].

11. Conclusion

As sepsis in children continues to take lives of children, especially in economically developing countries, it will continue to be the focus of attention for physicians, scientists, and the public. Although there are a few newer antibiotics in the pipeline, other novel therapies hold promise for overcoming this “cytokine storm disease” in near future.

Author details

Selim Öncel

Address all correspondence to: selimOncel@doctor.com

Division of Pediatric Infectious Diseases, Department of Pediatrics and Child Health, Section of Internal Medical Sciences, Kocaeli University Faculty of Medicine, Kocaeli, Turkey

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