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Sepsis in children: A narrative review

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Abstract

Sepsis, a systemic inflammatory response to infection, is a significant global child health concern with rising incidences and high mortality rates. The study describes how the main protective measure against sepsis is immunization, demonstrating its effectiveness against many pediatric infections. The disease's rapid progression necessitates swift recognition and initiation of treatment, primarily using antibiotics. However, the etiology of sepsis in children varies and is influenced by age, comorbidity, and geographical location, with an increasing prevalence of multi-drug-resistant organisms complicating antimicrobial selection. Risk factors like immunosuppressive treatments, malnutrition, alcoholism, and diseases compromising immune status increase susceptibility to sepsis. Moreover, the likelihood is further exacerbated by invasive procedures, hospital stay length, and underlying chronic diseases. Sepsis pathophysiology encompasses significant cardiovascular disturbances, from a localized infection to mild systemic infection, to septic shock. Elevated lactate in patients, traditionally believed to reflect tissue hypoxia, also appears to be driven by aerobic glycolysis triggered by increased adrenergic tone. Profound endothelial changes during sepsis, including leukocyte adhesion increase, shift to a procoagulant state, vasodilation, and barrier function loss, lead to widespread tissue edema. The article concludes by underscoring the urgency of thorough research to improve understanding and develop more effective interventions against sepsis.

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Introduction

Sepsis is a clinical syndrome resulting from an irregular systemic inflammatory response to infection. It is characterized by a generalized pro-inflammatory cascade that can lead to widespread tissue damage. Severe sepsis encompasses a range of clinical severity, including septic shock and multi-organ failure. Sepsis is a leading cause of morbidity and mortality in children worldwide. International consensus guidelines define sepsis as the systemic inflammatory response syndrome plus the presence of suspected or proven infections (1).

The most extensive epidemiological reports on the incidence of severe sepsis in children come from cohort studies in the US. Two of these studies describe the annual incidence of severe sepsis in children (defined as under 20 years of age) admitted for acute medical stays at hospitals in seven states of the US. These studies show an increase in the annual incidence of severe sepsis during this period (from 0.56 to 0.89 cases/1000 children in all age groups). In these cohorts, the incidence of severe sepsis was found to be significantly higher in younger age groups (incidence in the newborn age group and in babies aged 1.5 years) (2,3).

Sepsis is a systemic response to infection. Therefore, the primary etiology can be linked to both the infecting pathogen and the host response. While any infection can accelerate sepsis, the most common pathogens are bacteria, viruses, and fungi. The type of pathogen varies according to host factors such as age, comorbidity, and geographic location (4).

The main method of primary protection in sepsis is immunization. Immunization for many community-acquired pediatric infections has proven to be highly successful and cost-effective. Immunization has resulted in the global eradication of smallpox and a significant decrease in the prevalence of many infectious diseases (such as polio, rubella, tetanus, diphtheria, and measles). Advances in biotechnology have led to new and improved vaccines, including vaccines against Haemophilus influenzae type b, Neisseria meningitides (type C), and Streptococcus pneumonia (5).

Because the disease can rapidly progress to organ failure, shock, and death, sepsis should be considered a time-critical emergency. Therefore, rapid and early recognition of the condition is mandatory. It has been shown that timely antibiotics and other supportive treatments improve the outcome and early aggressive treatments should be initiated when sepsis is suspected. Generally, sepsis should be suspected if there is any change in the normal observation pattern of the patient in any acute illness or in the newborn population (including premature babies). While laboratory tests (such as blood cultures and biomarkers) can help confirm or support the diagnosis, the diagnosis should initially be made clinically (6).

Etiology

The causes of sepsis in the pediatric population are somewhat different from those attributed to adult sepsis. Early-onset neonatal sepsis, within the first 72 hours of life, is most likely due to Group B Streptococcus (GBS), Escherichia coli, Klebsiella spp., Enterobacter spp., and Listeria monocytogenes. After the first 72 hours of life, late-onset neonatal sepsis is most commonly due to coagulase-negative staphylococci, gram-negative bacilli, Enterobacteriaceae, and both methicillin-sensitive and methicillin-resistant Staphylococcus aureus. In older children, the most common etiologies are Staphylococcus, Streptococcus, Pseudomonas, and Meningococcus (7). The emergence of multi-drug resistant organisms, particularly in the intensive care unit (ICU), necessitates special attention and careful selection of antimicrobials. Data show increased mortality in infections secondary to multi-drug resistant organisms (8).

Epidemiology

Sepsis is a serious health problem worldwide with high mortality and morbidity rates. Although sepsis is more common in developed countries, the mortality rate is decreasing but still high. In pediatric intensive care units in North America, Europe, Australia, and New Zealand, 6-8% of patients have been treated for sepsis, and mortality rates of 21-32% have been reported (9). Sepsis was treated in 15-16% of patients in Asia and South America, with mortality rates varying between 11-40%. In South Africa, 25% of patients have been treated for sepsis, with 40% of these patients dying. The incidence of sepsis also varies by region. In the United States (US), 75,000 pediatric patients are treated each year for severe sepsis, with an incidence of 1/1000. Since the mid-1990s, the incidence has increased, with rates of 4.4% in patients treated at children's hospitals and 7% in pediatric intensive care units. In China, there are 360,000 annual admissions with an incidence of 1.8/1000. Respiratory tract infections are responsible for two-thirds of all severe sepsis cases worldwide. Most of these infections can be prevented by immunization. Since the 1960s, death rates from severe sepsis and

septic shock have decreased from 97% to 4-10% and 13-34% respectively. Data regarding the epidemiology and incidence of sepsis in the pediatric or adult age group in our country is insufficient (1-3,10,11).

Risk Factors

The list includes factors that increase the risk of sepsis, such as (1,2,6,9,12,13):

- Increasing use of cytotoxic and immunosuppressive agents,
- Malnutrition,
- Alcoholism,
- Malignancies,
- Diabetes,
- Increasing numbers of transplant recipients and transplant procedures,
- Increasing number of diseases that jeopardize immune status,
- Acquired Immune Deficiency Syndrome,
- Increasing use of aggressive invasive procedures in patient management and diagnosis,
- Increasing numbers of resistant microorganisms.
- Preterm infants,
- Newborns,
- Infants,
- Black race,
- Underlying chronic diseases (congenital or acquired immune deficiency, HIV infection, malignancies, chronic liver or kidney failure, chronic obstructive pulmonary disease, diabetes, diseases like sickle cell anemia with splenic dysfunction),
- Conditions leading to chronic comorbidities (uncorrected congenital heart diseases, patients with paralysis and encephalopathy with frequent aspiration pneumonia, short bowel syndrome, etc.),
- Urinary system anomalies leading to frequent urinary tract infections,
- Extended hospital stay and treatment history,
- Severe injuries (major trauma, burns, penetrating injuries),
- Large surgical incisions,
- Invasive placement of prosthetic devices (endotracheal tube, vascular catheter, urinary catheter, chest tube, etc).

Pathophysiology

As sepsis progresses from a localized infection to mild systemic infection, and then to septic shock, the cardiovascular system undergoes significant disturbances well-known to intensive care practitioners. With the widespread use of pulmonary artery catheters in the 1980s, it became evident that most patients with sepsis have normal or high cardiac output in conjunction with low systemic vascular resistance, even after intravascular volume has been restored (13). Preservation or increase in cardiac output occurs despite acute biventricular dysfunction, which can persist for over a week. Elevated lactate in these patients predicts mortality. Traditionally, this has been thought to reflect tissue hypoxia as a result of hypoperfusion. This theory has driven much of the therapeutic focus on increasing systemic oxygen delivery in a high normal cardiac output environment over the last thirty years. Remarkably, alternative theories for sepsis-induced hyperlactemia, such as aerobic glycolysis driven by increased adrenergic tone, have also been developed. The endothelium, which covers an area of approximately 1000 m2, can be considered an organ with significant roles in regulating vasomotor tone, the movement of cells and nutrients into and out of tissue, coagulation system, and internal balance (14,15). In sepsis, profound changes occur in the endothelium, including increased leukocyte adhesion, shift to a procoagulant state, vasodilation, and loss of barrier function, all leading to widespread tissue edema (15).

The normal host response to infection is a complex process that localizes and controls bacterial invasion while initiating the repair of injured tissue. It involves the activation of circulating and fixed phagocytic cells and the production of proinflammatory and anti-inflammatory mediators (16). Host response to infection is initiated when innate immune cells, particularly macrophages, recognize and bind to microbial components. This can happen in several ways (17,18). Pattern recognition receptors (PRRs) on the surface of host immune cells can recognize and bind to the pathogen-associated molecular patterns (PAMPs) of microorganisms (19). PRRs can also

recognize endogenous danger signals called alarmins or danger-associated molecular patterns (DAMPs). Triggering receptor (TREM-1) expressed on myeloid cells and myeloid DAP12-associated lectin (MDL-1) receptors in host immune cells can recognize and bind to microbial components (16,20).

Conclusions

Sepsis is a complex, inflammatory response to infection, causing a significant burden on global child health due to escalating incidences and associated high mortality rates. The mainstay of sepsis prevention is immunization, whereas timely recognition and rapid treatment, primarily with antibiotics, can significantly enhance prognosis. The pathogens vary based on host factors, and the growing emergence of multi-drug-resistant organisms necessitates careful antimicrobial selection. Addressing sepsis-related risk factors, such as underlying chronic diseases, invasive procedures, and extended hospital stay, could contribute to mitigating sepsis incidences. Comprehensive research to understand sepsis better and develop more effective interventions is crucial.

Conflict of interest

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