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Review

Antimicrobial Therapy in Paediatric Sepsis and Treatment Strategy

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Abstract

Sepsis is a complex and severe disorder that significantly affects the pediatric population and is responsible for approximately 7.5 million deaths annually. Sepsis is a potentially fatal reaction to infection that greatly increases neonatal and pediatric morbidity and mortality globally. Sepsis can also lead to more severe forms, such as severe sepsis, septic shock, multiorgan failure, and refractory septic shock in cases with known or suspected infections. Early diagnosis, prompt administration of the proper fluids to restore adequate tissue perfusion, and empiric antimicrobial therapy to protect against suspected infections are the main tenets of therapy. If, after initial fluid resuscitation, tissue perfusion and hemodynamics are unstable/insufficient, vasoactive medications are advised. Ampicillin and gentamicin are recommended for use in early onset neonatal sepsis while third generation cephalosporins are also included in the treatment regime in case of late-onset sepsis. A broad-spectrum antibiotic that treats both gram-positive and gram-negative bacteria is advised for 1 month above children, but the choice of antibiotic depends on the clinical presentation, such as pneumonia, bloodstream infection, intra-abdominal sepsis, or meningitis that resulted in septic shock. A delay in antimicrobial administration is linked to increased mortality rate hence, guidelines recommend antimicrobial administration within 1 hour after confirmation of sepsis. There is substantial evidence to support the notion that rapid antimicrobial initiation and selection are essential components of the therapy of patients with severe illnesses. The purpose of this research is to review the available information about antimicrobial therapy in paediatric sepsis and treatment strategy.

Keywords: *sepsis, pediatric, antimicrobial, therapy*

Introduction

Sepsis is the leading cause of death in children globally, accounting for an estimated 7.5 million deaths per year. Two or more systemic inflammatory response syndrome criteria, a confirmed or suspected invasive infection, cardiovascular dysfunction, acute respiratory distress syndrome, or two or more organ dysfunctions are all considered to be signs of severe sepsis in children (1). Around the world, approximately 10%–25% of hospitalizations to pediatric intensive care units are due to severe sepsis and septic shock, up to 30%- 50% of patients are admitted directly from the emergency department, while the other patients are admitted from other hospital wards. Given that 77% of patients have at least one comorbid disease, hence pediatric chronic disorders are an important risk factor. Children around the world are affected differently by sepsis in terms of mortality and morbidity. Available data from studies reveals a mortality rate of 25% and long-term sequelae in 20% of survivors (2).

In the context of infection, sepsis is a spectrum of diseases characterized by a systemic inflammatory response syndrome that can progress to septic shock and malfunction of the cardiovascular and organ systems. It results in severe pediatric morbidity and mortality and is the last common inflammatory pathway for the majority of infectious disease-related deaths. Delays in presentation and delays in diagnosis have been found to be risk factors for poor outcomes, both of which can have a substantial impact on the identification and initial management of children with sepsis (3). Recent recommendations suggest development of an institution-specific recognition bundle to use as a trigger tool to screen patients for septic shock. Temperature abnormalities such as hyperthermia or hypothermia, altered mental status including confusion, drowsiness, inconsolability, irritability, unresponsiveness, and evidence of altered perfusion are among the symptoms seen in pediatric and newborn patients. It should be highlighted that hypotension is a late indication of pediatric/neonatal septic shock, typically appearing when patients are on the verge of cardiovascular collapse (4). Airway reassurance initial volume resuscitation, antimicrobial therapy, and cardiovascular support are the cornerstones of sepsis treatment, along with proper oxygenation and ventilation if required. In the absence of a volume response during the first hour, the administration of vasoactive medications like epinephrine or norepinephrine is required (5).

As per the evidence, early and rapid antimicrobial treatment is essential to improve patient outcomes in sepsis and septic shock. Administration of broad-spectrum antibiotics within an hour of presentation is recommended. Empiric broad-spectrum antimicrobials should be chosen based on local antimicrobial resistance patterns and known epidemiology, taking into account the patient's immunocompromised state, recent hospital admissions, presence of any indwelling devices or catheters, and known colonization with particular pathogens (6). The choice of an antimicrobial depends on the potential etiologic organisms and the various patterns of antibiotic susceptibility that these organisms exhibit. Penicillin and an aminoglycoside, most frequently ampicillin and gentamicin, are indicated as the first line of treatment, while when staphylococcal septicemia is suspected, adding vancomycin is advised. According to the outcomes of susceptibility tests, the use of third-generation cephalosporins or acylaminopenicillins may be appropriate for newborn sepsis caused by gram-negative bacteria that are resistant to aminoglycosides (7). The purpose of this research is to review the available information about antimicrobial therapy in paediatric sepsis and treatment strategy.

Methodology

This study is based on a comprehensive literature search conducted on December 14, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about antimicrobial therapy in paediatric sepsis and treatment strategy. There were no restrictions on date, language, participant age, or type of publication.

Discussion

The advantages of early detection, treatment, and shock reversal employing bundled sepsis care go beyond mortality declines. After the implementation of bundled care, numerous pediatric studies have shown decreased hospital lengths of stay and decreased rates of acute renal damage. Children who encountered antibiotic delays of more than 3 hours had a nearly 4-fold risk of mortality in the pediatric intensive care unit, and delays in receiving antimicrobial medication are linked to higher mortality. According to various other research studies, the risk of dying increases by more than two times for every hour

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that a shock lasts. Furthermore, a number of pediatric studies have examined the association between the timing of antibiotic administration and fluid resuscitation using protocol-driven care and patient-level outcomes, leading to continuing adjustments to institutional, national, and international guidelines (8).

Evidence from literature

Ampicillin and gentamicin should be used in cases of newborn sepsis that present with an early onset that is within 72 hours. Similar broad-spectrum antibiotics are used in late-onset newborn sepsis which refers to more than 72 hours of time, but third generation cephalosporins, such as cefotaxime, are also included. Instead of ampicillin, vancomycin is used for the management of catheter-associated infections. A broad-spectrum antibiotic that treats both gram-positive and gram-negative bacteria is advised for children older than one month, but the choice of antibiotic depends on the clinical presentation, such as pneumonia, bloodstream infection, intra-abdominal sepsis, or meningitis that resulted in septic shock. According to international recommendations, antibiotics should be administered within an hour after the diagnosis of septic shock since delaying treatment is linked to a high death rate. There is ample evidence to support the idea that in the treatment of patients with severe illnesses, the antibiotic should not only be chosen wisely but also promptly administered (9). Aneja et al. described that ampicillin and gentamicin are used in combination as the empiric treatment for late-onset sepsis in term or late preterm infants admitted after 7 days. Gentamicin is substituted with cefotaxime every 8 hours if meningitis is suspected. A lumbar puncture should be carried out as soon as the child is stable. Vancomycin is preferable to ampicillin if there has been a history of protracted hospitalization or if the child has a central venous catheter. Vancomycin and gentamicin/cefotaxime are the recommended empiric treatments in this situation. The switch to vancomycin expands protection against Coagulase-negative staphylococcus and Staphylococcus aureus. Nafcillin should be used to finish the Methicillin-resistant Staphylococcus aureus antibiotic course once sensitivities have been identified. Following the resolution of bacteremia, clindamycin is now advised for susceptible Methicillin-resistant Staphylococcus aureus isolates for the management of newborns (10).

The significance of early administration of antimicrobial therapy can be described by the findings of study by Weiss et al. who reported that with each hour that passed between sepsis diagnosis and antibiotic administration, a rising risk of mortality was seen, however this didn't become statistically significant until 3 hours. The odds ratio for pediatric intensive care unit death was 3.92 (95% confidence interval (CI), 1.27-12.06) for patients who received their initial and first suitable antimicrobials more than three hours late, and 3.59 (95% CI, 1.09-11.76) for those patients. The odds ratio for pediatric intensive care unit mortality rose to 4.84 (95% CI, 1.45-16.2) and 4.92 (95% CI, 1.30-18.58) for more than 3-hour delays to initial and first suitable antimicrobials, respectively, once illness severity was taken into account. Additionally, fewer organ failure-free days were linked to initial antimicrobial therapy that was delayed by more than 3 hours. In pediatric sepsis, delayed antibiotic therapy was a risk factor on its own for mortality and protracted organ failure (11).

Similarly, Han et al. demonstrated in their findings that when compared to patients who got antimicrobials within 1-3 hours of sepsis diagnosis, there was an increase in one-year mortality in patients who received antimicrobials greater than 1 hour or 3 hours. Antimicrobial therapy greater than 1 hour was also linked to higher one-year mortality for the subset of patients who survived index pediatric intensive care unit stay (12). Likewise, Sankar et al. concluded that in children with sepsis, severe sepsis, and septic shock, delayed antimicrobial delivery after 1 hour of confirmation was linked to greater fatality rates. In these children, antimicrobials should be given within the first hour, along with other resuscitative measures (13). Khanthathasiri et al. revealed a successful single-dose empirical antimicrobial approach in a busy emergency department with a focus on prompt administration of the first effective antimicrobial dose to children with suspected sepsis. This method shortened the period between arrival at the hospital and the start of the antimicrobials and enhanced the outcomes of pediatric sepsis. The single-dose empirical antimicrobial approach is straightforward, safe, and workable for high-load emergency departments with just a small amount of antibiotic misuse (14).

The premise that a collection of therapies, referred to as a care bundle, is more likely to produce favourable results has gained widespread acceptance. A sepsis care bundle involves basic resuscitation and treatment procedures such as taking a blood culture, starting antibiotics, and giving fluid bolus to children with sepsis-related organ dysfunction within 180 minutes and those with septic shock within 60 minutes. Blood culture collection and antibiotic administration are

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acknowledged bundle components based on data and biological reasoning. However, the excessive consumption of fluids has recently drawn criticism. In cases of suspected sepsis, immediate large volume fluid delivery has traditionally been the cornerstone of care. Recent observational studies suggest that high volume fluid treatment in sepsis may be harmful to both adult and pediatric groups. There are currently many methods for treating refractory septic shock, including extracorporeal treatments, immunomodulation, and hydrocortisone (15).

Sharma and kumar stated that as soon as severe sepsis and septic shock are identified, intravenous antibiotics should be given. Selecting broad-spectrum antibiotics that have one or more agents active against potential bacterial or fungal infections and have good penetration into the suspected source is essential. To maximize effectiveness, prevent resistance, avoid toxicity, and cut costs, antimicrobial therapy should be re-evaluated every day. When treating septic shock, combination therapies shall be considered for Pseudomonas infections in patients with neutropenia. Combination therapy should only be sustained for three to five days at most, and de-escalation should start once susceptibilities are available. Antibiotic medication is normally only administered for 7 to 10 days. If the reaction is sluggish, if surgical source control is insufficient, or if immunologic shortcomings are obvious, a longer time is taken into consideration (16).

The immediate use of suitable, broad-spectrum antimicrobials is the foundation of pediatric sepsis management. Bacteriostatic antimicrobials are typically favoured over bactericidal antimicrobials for sepsis. Linezolid and clindamycin are examples of bacteriostatic antimicrobials that will slow the growth of the organism but rely on the patient's immune system to completely eradicate it from the body. Bactericidal substances, such as -lactams, on the other hand, work independently of the immune system to eradicate germs. To stop the emergence of antimicrobial resistance, the antibiotic spectrum must be constrained together with the length of antibiotic therapy. Additionally, this method reduces the possibility of a superinfection with bacteria that are extremely resistant, like vancomycin-resistant Enterococcus (17).

With research demonstrating improved outcomes in critically ill patients with severe sepsis, de-escalation is a recommended technique to avoid antimicrobial-related adverse effects, additional expenses, and the emergence of antimicrobial resistance. The appropriateness of the antimicrobial medication is assessed at 48–72 hours, depending on the clinical status, response to management, and microbiological data, and therapy is altered or narrowed as necessary. De-escalation can be expanded to stopping antibiotic therapy if data refutes the presence of a bacterial illness (18-20). Emerging resistance calls for a well-tailored approach to the antimicrobial management of pediatric sepsis, as does the growing importance of immunocompromise, prior exposure to toxic medicines such as chemotherapy, and other factors. A primary option covering a broad antibiotic range, such as a fourth-generation cephalosporin or a carbapenem, should be recommended in children with a high risk of resistant gram-negative infections. Third-generation cephalosporins are not advised for invasive Enterobacter infections due to rising clinical data showing their treatment failure for Enterobacter species. Alternatives include broad-spectrum beta-lactam/beta-lactamase inhibitor combinations (21).

Polin stated that broad-spectrum antibiotics are the ideal therapy for neonates with suspected early-onset sepsis. Antimicrobial treatment should be targeted after a pathogen has been identified unless synergism is needed. Recent research indicates an increased risk of late-onset sepsis, necrotizing enterocolitis, and mortality when preterm newborns get extended empirical treatment with broad-spectrum antibiotics. Antimicrobial medication should be stopped at 48 hours in clinical conditions where the likelihood of sepsis is low in order to lower these risks (22). The majority of sepsis treatment in contemporary pediatrics continues to be supportive. Although the development of potent broad-spectrum antibiotics has increased the ability to kill bacteria, the main focus of sepsis therapy is to support oxygen delivery and maintain homeostasis throughout the septic insult. However, because sepsis mortality is still too high, researchers are now looking for new treatments that modulate the septic cascade in an effort to stop or slow the sepsis syndrome (23). Prospective randomized studies that assess both short-term and long-term outcomes of antimicrobial therapy after admission should be the main emphasis of pediatric sepsis research in the future since the literature available has limited clinical studies. Additionally, further clinical research shall focus on the development of new treatment modalities.

Conclusion

The global impact of pediatric sepsis is still quite significant in today’s modern era of medicine. Accurate

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and prompt diagnosis is the first step in treating sepsis. Antimicrobial therapy is the foundation of management of pediatric sepsis. The most crucial aspects of sepsis treatment are rapid and vigorous management with intravenous fluids, antimicrobials, and vasoactive drugs, which enhance outcomes.

Disclosure

Conflict of interest

There is no conflict of interest

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Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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