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Sepsis: A Systematic Review of Antibiotic Resistance and Antimicrobial Therapies

Jasmine Macias*, Omar Kahly, Roshana Pattik-Edward, Sarah Khan, Amad Qureshi, Alisha Shaik, Arta Shala, Darsh Shah

Socratic Med Inc., New York, USA
Email: *jasmac1780@gmail.com

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Abstract

Sepsis is a medical emergency that depicts the body's systemic immune reaction to an infectious process that could result in organ dysfunction and death. Early sepsis pathogen identification and early delivery of antimicrobial therapy result in better clinical outcomes for patients diagnosed with sepsis and septic shock. **Method:** Systematic reviews and meta-analyses that discussed sepsis pathogen identification, antibiotic resistance and timing in the treatment of sepsis were taken into account irrespective of the approach of the included studies, quantitative or qualitative. This literature review gathers data from twelve primary studies to perform a systematic review and evaluate existing empirical antibiotic therapies in order to treat the various degrees of sepsis and minimize antibiotic resistance. The remaining reviews, case studies, etc., were used as supplementary references. The studies compiled data from laboratory tests including lactate levels, fluid resuscitation, and diagnostic diagnostics like the SOFA score. **Results:** This paper identifies multiple factors that must be taken into account when treating individuals with sepsis. Prior to the administration of broad-spectrum empiric antibiotics, the severity and morbidity of the disease must be addressed. Excessive antibiotic usage has been associated with increased sepsis hospitalized mortality rates, and thus it is crucial to minimize antibiotic misuse in non-septic patients. This can be accomplished by differentiating between Gram-negative and Gram-positive bacteria, the purpose of biomarkers and identifying the antibiotic resistance pathway. Many patients from low economic statuses may experience difficulties accessing healthcare services and resources for sepsis treatment when diagnosed with sepsis. Additionally, through educational efforts, promoting awareness of sepsis and the relevance of timing in sepsis therapy can help dispel misconceptions about the illness and minimize sepsis patients from receiving insufficient care.

Keywords

Timing, Antibiotics, Sepsis, Pathogen, Resistance

1. Introduction

1.1. Foundations of Sepsis

The Centers for Disease Control and Prevention (CDC) defines sepsis as the body's overreaction to an infection that rapidly spreads to other organs, which could lead to a life-threatening situation for the patient (CDC, 2021). Sepsis manifestations include excessive perspiration, pain or discomfort, shortness of breath, increased blood pressure, and chills (CDC, 2021). Sepsis can be broken down into four progressive periods of severity: systemic inflammatory response syndrome (an excessive immune response that is occasionally considered the prelude to sepsis), sepsis, severe sepsis, and septic shock [1]. There is a proportional relationship between the severity of sepsis and the mortality rate [2]. Demographics documented by the CDC for sepsis infections include the elderly, those with compromised immune systems, chronic diseases, recent illnesses, and sepsis survivors. Bacteria and viruses are primarily accountable for causing these infections. However, it can be difficult to treat if these pathogens are able to thrive and propagate even with antibiotic or antimicrobial drugs [3]. Sepsis affects 1.1 to 2.4 per 1000 individuals each year, with 20 to 42 percent of patients dying in hospitals, with these figures possibly underestimating the involvement of hospital-acquired infections [4]. Antibiotic treatment for the initial 24 to 48 hours is primarily empirical (*i.e.*, given without corroboration of the causative pathogen or its susceptibilities), and it is widely known that evidence-based antibiotic treatment minimizes mortality [5]. As a result, clinicians seek to provide optimal empirical antimicrobial treatment for hospitalized patients with sepsis, often at the expense of administering superfluous antibiotics. This excessive type of therapy is linked to the development of antibiotic resistance. Bacteria develop antimicrobial resistance through adaptation. The ability of bacteria to adapt and react to environmental stressors, such as antibiotic stress, depends on their genome's plasticity. Antibiotic resistance is a long-standing phenomenon that develops from the interactions between organisms and their surroundings. Since most antibiotics were naturally produced by bacteria and fungi for millions of years, microorganisms have developed ways to resist their effects, thrive, and proliferate [6]. Consequently, many bacteria are naturally resistant to one or even a majority of antibiotics. The development of acquired resistance occurs by horizontal gene transfer (HGT), external genetic acquisition from neighboring resistant organisms, or gene mutations [7]. HGT allows for the transmission of antibiotic resistant genes (ARGs), which makes the bacteria highly pathogenic [8]. Microbes become resistant to antibiotics by controlling the concentration of the drug in their cells. They accomplish this by either regulating the influx and

efflux of drug particles, causing conformational changes within the active site(s) of the drug, or by adapting themselves to avoid interactions with the antibiotic.

1.2. Differences in Gram Negative versus Gram Positive Activities Involved in Sepsis

The bacteria that cause these infections are categorized into two groups: gram-negative bacteria and gram-positive bacteria. Gram-negative bacteria have a considerably thinner peptidoglycan cell wall and stimulate the immune system with liposaccharides. Gram-positive bacteria have a much thicker layer of peptidoglycan, but use lipoteichoic acids instead to induce a weaker immune response than liposaccharides as toxins [9]. Of these two groups, it is found that gram-positive bacteria appear more often in sepsis cases [10]. According to a review by Ramachandran, gram negative bacteria are more lethal and have the capability to cause more proinflammatory cytokines to be released [11]. The more severe cases of sepsis are directly correlated to gram-negative bacteria as they are resistant to the antibiotics [2]. Gram-negative bacilli currently exceed gram-positive pathogens in ICU infections, according to a recent analysis of ICUs throughout the world that reported a comparable distribution of ESBL-producing gram-negative bacilli. Gram-negative bacteria's outer membrane is the primary cause of resistance to a wide range of antibiotics such as β-lactams and colistins. Most antibiotics must pass through the outer membrane to reach their targets; for example, hydrophobic drugs can pass through a diffusion pathway, while hydrophilic antibiotics must pass through porins. Gram-negative bacteria acquire resistance through modifying the hydrophobic characteristics of the outer membrane, as well as through changes in porins and other elements. Gram-positive bacteria lack this layer, making gram-negative bacteria more antibiotic-resistant than gram-positive bacteria. Immediate antibiotic therapy appears to be more important for gram-negative bacteria than gram-positive bacteria. This might be attributed to endotoxin-mediated sepsis in gram-negative bacteria, emphasizing the significance of prioritizing antibiotic therapy with gram-negative coverage in patients receiving more than one class of antimicrobials [11].

2. Methods

Search Strategy and Types of Data Collection

A systematic review was conducted employing previously published literature from sources such as NCBI, PubMed, BMC and NHI. The articles employed laboratory tests such as lactate levels, fluid resuscitation and diagnostic tests such as SOFA score in their data collection. Some studies dissected the difference between gram-positive and gram-negative bacteria as well as the various methods that gram-negative bacteria employ to acquire resistance.

Eligibility Criteria

Types of studies

All systematic reviews and meta-analyses that discussed sepsis pathogen identification, antibiotic resistance and timing in the treatment of sepsis were taken

into account irrespective of the approach of the included studies, quantitative or qualitative. Literature collection and analysis was performed on the basis of whether the articles attempted to validate/invalidate the notion that early antibiotic delivery will lead to the minimization of sepsis mortality and antibiotic resistance. The authors employed twelve primary studies which had the greatest degree of evidence and supported this investigation as a reference to perform the analysis. The remaining reviews and case studies were used as supplementary references. Studies that solely involved broad spectrum treatment were excluded from this literature review, as this procedure exacerbates conditions and gives rise to newer antibiotic resistant microbes rather than targeting the main source of infection to reduce the severity of clinical manifestations in sepsis patients.

Types of Participants

We took into account all systematic reviews and meta-analyses, independent of participant gender or age.

Types of Interventions

All systematic reviews and meta-analyses of interventions for the diagnosis, evaluation, or treatment of sepsis were taken into consideration.

Types of Outcome measures

Irrespective of the clinical parameters employed in this study, all systematic reviews and meta-analyses were included. Studies that did not provide information on results pertinent to the review were excluded. Particular emphasis was placed on outcomes of therapies that reduced the use of excess antimicrobial treatment as it exacerbates sepsis severity by reducing symptoms instead of targeting the origin of infection.

3. Results

3.1. Clinical Parameters of Sepsis That Lead to Empirical Therapy

The infecting pathogen is typically a bacteria, with gram-negative bacteria being the most commonly associated with severe sepsis and septic shock, with an occurrence of approximately 71,000 to 330,000 cases per year in the United States [12]. However, nonbacterial species can also produce clinical sepsis manifestations. Due to the variation in symptoms, there is no standard gold test for sepsis. Developing diagnostic criteria for sepsis has been challenging and is evolving over time. The systemic inflammatory response syndrome (SIRS) criteria were employed to make an early diagnosis. Temperature, heart rate, respiration rate, and white blood cell count anomalies are used to determine this criterion [13]. Patients with sepsis are classified as having a probable source of infection, as well as two or more of the four SIRS criteria in this method. SIRS criteria are not considered an accurate diagnostic test as many people have aberrations in these parameters that are unrelated to an infection or have an infection without concurrent sepsis. Other individuals with sepsis do not satisfy this criterion while exhibiting symptoms of organ failure. The sequential organ failure assessment (SOFA) score is currently used in the diagnosis of sepsis, in which the perfor-

mance of the organ system is evaluated on a scale of 0 to 4 based on six criteria reflecting the function of an organ system (respiratory, cardiovascular, renal, neurological, hepatic and hematological) measured by laboratory tests [14]. The requirements of the Systemic Inflammatory Response Syndrome (SIRS) consist of the following outcomes and ranges: Tachycardia, heart rate of >90 beats/min; Tachypnea, respiratory rate of >20 breaths/min; Fever or hyperthermia, temperature > 38˚C or <36˚C; Bandemia, leukopenia, or leukocytosis, where bandemia ≥ 10%, leukopenia < 4000/mm^3, and leukocytosis white blood cells > 1200/mm^3 [15].

A quick SOFA score (qSOFA) has been recommended as an alternative for more readily identifying at-risk patients and prompting clinicians to further assess for organ failure. A respiration rate of ≥22 breaths per minute, a systolic blood pressure ≤ 100 mm·Hg, and abnormal mentation are all qSOFA requirements [16]. This diagnostic approach is more credible than SIRS criteria in the identification of patients with sepsis, but it is more difficult to use and requires the calculation of laboratory results.

After taking into account much of the already existing literature, there is an overwhelming complexity that contributes to the clinical outcomes in treating sepsis. To emphasize the significance of timing during sepsis treatment, it was found that any delay in administering fluid resuscitation and antibiotics greatly decreased the survival rate of sepsis patients. In addition, each hour of delay in antibiotic administration led to an increased risk of mortality. When appropriate antibiotics are taken within the first hour of documented hypotension, the survival rates increase drastically up to 80%. Studies also point toward the importance for health care providers to follow the guidelines provided by the Surviving Sepsis Campaign (SSC), ensuring the best quality of care for sepsis-infected patients [17]. There is also an association between excessive or inadequate empiric antibiotic treatment and mortality. Sepsis patients who are resistant to antibiotic pathogens are more likely to have low survival rates when administered broad spectrum antibiotics, compared to patients who are not resistant to antibiotics [18]. Educational intervention regarding sepsis infection and control leads to a decrease in the mean time between the onset of sepsis and the start of antibiotic treatment [19].

3.2. Antibiotic Guidance Which Encompasses Antibiotic Timing, Adverse Effects of Antibiotics and Antibiotic Resistance

Blood cultures should be collected prior to antibiotic administration for patients with suspected sepsis. Two aerobic and anaerobic sets of blood cultures should be acquired from different sites if the patient's history and physical exam reveal a source of infection. After the identification of sepsis employing blood cultures, the SOFA score, and other diagnostic tests, antimicrobial therapy should be started immediately to eliminate bacteria, especially gram-negative bacterium, so that the infection does not increase in severity. The landmark study by Kumar *et al.* [20] found that each one-hour delay in antibiotic delivery increased sepsis

mortality by 7.6%. Ferrer *et al.* [17] discovered that each hour of antibiotic delay resulted in a linear improvement in sepsis mortality. In patients with sepsis, one-hour antibiotic timing reduced mortality by 9.5 percent, from 33.1 percent in patients who got delayed PREVIEW 4 antibiotics to 24.6 percent in those who received antibiotics within one-hour [17] [21]. Antibiotic treatment has been proved to be a lifesaving intervention during the "golden hour" of severe sepsis and/or septic shock diagnosis, according to Van Zanten [21] and the Serving Sepsis Campaign. For certain patients, rapid antimicrobial treatment is critical, although a significant portion of patients originally diagnosed with sepsis have noninfectious causes. For this subset of the population, rigorous time-to-antibiotic regimens risk antibiotic resistance. For certain patients, rapid antimicrobial treatment is critical, although a significant portion of patients originally diagnosed with sepsis have noninfectious causes. For this subset of the population, rigorous time-to-antibiotic regimens risk antibiotic resistance. Selecting the ideal balance between ensuring immediate antibiotics for patients with severe sepsis and septic shock as well as enabling clinicians some time for rapid analysis to mitigate the chances of defensive medicine and antibiotic-associated detriments for patients who are not infected requires a detailed understanding of the link between time to antibiotics and mortality in patients with a plausible sepsis diagnosis. Hence, the above studies evaluated factors such as lactate levels to observe a link between early intravenous antibiotic therapy and the minimization of sepsis mortality and found that rapid antibiotic delivery within the hour will lead to the minimization of sepsis mortality in patients who are confirmed to have sepsis. However, patients with an indeterminate diagnosis will suffer from the adverse effects of antimicrobial therapy such as antibiotic resistance.

Previous antibiotic use by a patient may increase the risk for microbial resistance if the same antibiotics are repeatedly administered in a prospective treatment. Knowledge of the patient's history of consumption of antibiotics, is not diagnostically relevant, but is important to consider when choosing a treatment regimen [22]. Antibiotics have the potential to harm, but they can be beneficial in eliminating pathogens if administered appropriately. Niederman [23] and his team claim that the manner in which antibiotics are delivered to a patient can determine their effectiveness while treating sepsis. He and his team assert that there is a distinction between early empirical antibiotic treatment and inappropriate antibiotic treatment in which the latter can cause an increased risk of colonization and infection with antibiotic resistant pathogens, therefore increasing the risk of mortality [23]. To help guide sepsis therapy, biomarkers were suggested by Niederman. They found that procalcitonin was an effective biomarker, reducing antibiotic use in septic patients [23]. Immune response biomarkers are of relevance for evaluating antibiotic treatment efficacy because the direct evaluation of bacterial disease load during clinical infection is generally not achievable and because the effects of infection-induced inflammation contribute to eventually reported efficacy [24]. Pathogen associated molecular patterns (PAMPs) found in bacteria stimulate an immune response that leads to the formation of

various immune response biomarkers that include interactions across multiple cell types and tissues. Multiple host immune response biomarkers have been linked to treatment outcomes like death, inpatient care, and duration of antimicrobial therapy, with the substantial body of research concentrating on patients with severe sepsis and significant respiratory tract infections (RTIs). Notably, using such biomarkers to limit and/or optimize antibiotic use could also decrease the likelihood of resistance developing [25].

3.3. The Influence of Socioeconomic Status on Sepsis Outcomes

Socioeconomic variables play a significant role in the course of sepsis treatment and sepsis-attributable mortality. The efforts to minimize the time required to administer antibiotics may result in unforeseen consequences and expenses. Such harms might arise from a greater proportion of patients receiving antibiotics unnecessarily due to factors such as an inadequate amount of time, equipment, and available resources for clinicians to evaluate alternative diagnoses for the patient's presentation [26]. Within resource and staff-constrained settings like the emergency department or ICU in low-income communities, the focus on antibiotic timing could also result in decreased attention to and investment in other time-sensitive patient needs [27]. A study performed by physician Galiatsatos and his team showed that in Baltimore City, sepsis-related mortality was greater in low-income neighborhoods than in higher-income ones [28]. Poverty in the neighborhood, a lack of insurance, and a decreased rate of formal education were all found to be independently linked to sepsis-attributed morbidity.

The 2011 Neighborhood Health Profile Reports of Baltimore City provides data for 55 communities within the city limits. The study's findings show that neighborhoods with lower versus higher household income demonstrated higher rates of death from sepsis (4.2 (IQR 3.48 - 5.10) versus 2.9 (IQR 2.25 - 3.35) respectively, $p = 0.0002$). Median household income and family poverty rate were significantly correlated with the mortality rate from sepsis [29]. Having insurance may reduce sepsis-related mortality through prevention of infections (e.g., by making immunizations more accessible), prevention of organ malfunction and/or maintenance of concomitant disease (e.g., diabetes, heart disease, regular diagnostic checkups), and expedited medical attention before organ damage/dysfunction has occurred (PAP smear, mammography) [30]. Although vaccination rates were not reported in this study, the CDC reported that minorities (Black, Hispanic, other or multiple races) had significantly lower pneumococcal vaccination rates in 2018 than non-Hispanic white individuals in both the 18 - 64 age group with increased risk and the >65 age group. Lack of health insurance, perceptions, and attitudes about vaccination are all factors that contribute to racial/ethnic differences in vaccine uptake [31]. Multiple authors in the sepsis literature have suggested therapies that target sepsis prevention through optimization and prevention of comorbidities, as well as immunizations.

3.4. Antibiotic Resistance Mechanism

The consequence of empirical antibiotic therapy is multidrug antimicrobial resistance and the scarcity of novel antimicrobials to yield efficacious and safe treatments for sepsis patients. Multidrug resistance is caused by the concurrent activation of numerous resistance mechanisms upon antibiotic exposure. Some mechanisms include the synthesis of chromosomally encoded ESBL, reduced permeability through loss of porin channels, and activation of multidrug efflux pumps [32]. Furthermore, the transfer of plasmids and migratory elements containing multiple resistance genes contributes to the development of multidrug-resistant traits. Antimicrobial resistance in gram-negative bacteria is extremely difficult to regulate. Of the famous ESKAPE pathogens identified as the most important emerging threats in antimicrobial resistance (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter* species, *Pseudomonas aeruginosa*, and *Enterobacter* species), the majority are gram-negative bacteria [33]. Common broad spectrum antibiotic classes administered upon sepsis identification include Carbapenems, Colistin,Tigecycline and Fosfomycin. Gram-negative bacteria can develop resistance to a single class or many classes of antibiotics through a variety of mechanisms such as β-lactam and Carbapenem resistance.

Resistance to cephalosporins and aztreonam is induced by the synthesis of extended-β-lactamases (ESBLs), enzymes that inhibit antibiotic activity by breaking the amide bond of the β-lactam ring. TEM, SHV, CTX-M (found in Enterobacteriaceae), and OXA (found in Pseudomonas isolates) are the most common ESBL families; they all hydrolyze oxyimino-β-lactam substrates and are highly receptive to β-lactamase inhibitors. In the United States and Europe, the increasing prevalence of CTX-M enzymes has been linked to the ST131 (0:25:H24) *E. coli* clone that accounts for most of the spread of isolates resistant to fluoroquinolone and broad-spectrum β-lactam antibiotics [34].

The synthesis of carbapenemases—ESBLs capable of hydrolyzing a broad range of β-lactam antibiotics, such as cephalosporins, and carbapenems—is the primary method of carbapenem resistance. Klebsiella pneumoniae carbapenemases (KPC) are the most clinically significant of the class A carbapenemases. These bacteria are plasmid-based, are resistant to all β-lactams, and can be transmitted to other gram-negative bacteria, such as Pseudomonas, which have all been retrieved from clinical isolates of hospitalized patients. Class D carbapenemases belong mostly to the OXA-type family and are found primarily in P. aeruginosa and Acinetobacter species. Carbapenem resistance can also occur through other mechanisms, such as impermeability and efflux, especially in Pseudomonas isolates [35]. Production of cephalosporinases such as AmpC enzymes combined with a reduction in antimicrobial diffusion across bacterial membranes through alterations in the genes regulating porin channels can also confer carbapenem resistance in gram-negative bacteria [36].

4. Literature Review

In this paper, the literature in the field of empirical antibiotic therapies for the

treatment of sepsis is classified into four categories as listed below:

1) Delay in fluid resuscitation, antibiotic administration and low-quality care in hospitals leads to higher mortality rates;

2) Socioeconomic status is a barrier to acquiring proper treatment after sepsis diagnosis;

3) Awareness and Education for Patients and Healthcare workers;

4) Inadequate and excessive antibiotic administration in antibiotic resistant patients leads to lower levels of survival and antibiotic resistance.

4.1. Improper Antibiotic Administration and Fluid Resuscitation Associated with Increased Mortality Rates

Multiple studies point toward the association between the timing of empiric antibiotics and mortality from a sepsis infection. Physicians treating patients with sepsis follow the guidelines outlined by the Surviving Sepsis Campaign (SSC), which recommends the administration of broad-spectrum antibiotics within ~1 - 3 hours after diagnosis of sepsis shock or severe sepsis. The more time that progresses after the first hour of sepsis diagnosis, the higher the linear increase in the mortality rate for patients suffering from sepsis shock [17]. Within the first six hours of severe sepsis diagnosis, the risk of hospital mortality increases by 7.6% every hour when antibiotics are not administered to the sepsis patient [20]. This alludes to the fact that timing is critical for the administration of antibiotics to patients suffering from severe sepsis or sepsis shock. In addition to empiric antibiotics, preventing the delay in the timing of fluid resuscitation, organ support and improving the quality of care in hospitals leads to increased survival rates of sepsis patients [17]. Future studies focusing on the implications of timing in antibiotics and fluid resuscitation should focus on whether there is a relationship between disease morbidity and age when antibiotic administration is delayed. In addition, further studies should focus on whether there is a significant difference in mortality rates between sepsis patients from different countries so that factors such as race and ethnicity can be monitored for confounding variables in sepsis survival rates. These studies can also point toward how the quality of care in hospitals from different parts of the world affects mortality rates of sepsis patients.

4.2. Socioeconomic Barriers to Sepsis Treatment

Lower SES usually indicates whether there can be some sort of difficulty or hindrance to accessing healthcare. Galiatsatos and his team sampled communities around the city of Baltimore to determine the relationship between mortality by sepsis and community socioeconomic status. Results suggest that lower-income neighborhoods have a higher mortality rate, specifically those suffering from poverty. Medication, treatment, and other therapies can be costly and getting help for even the simplest of care can accumulate per visit. Without any financial aid or labor opportunities, reducing the cost of treatment will prove insignifi-

cant. Education was found to have a great inverse correlation with the mortality rate of sepsis. Knowledge and awareness about sepsis and antibiotic resistance can make a difference in the effectiveness of the care given and how likely the patient is to recover from sepsis. Being informed of options that alleviate the financial burdens of sepsis treatment and having access to places where a higher quality of care is given allows patients to have a higher chance of survival. Other factors such as gender, age, and race are statistically insignificant when considering mortality by sepsis. The biological and chemical applications of sepsis apply to nearly every kind of organism, as bacteria is universally known to cause a great ordeal of infections that can be lethal in many conditions including those that can be considered extreme. A multivariable analysis done by Paul and other researchers confirms this finding as well, especially with age [4]. The research done by the other researchers does not include socioeconomic status or accessibility to healthcare resources as a factor that may potentially affect the lethality of sepsis and the outcome of treatments. It could be that certain aspects of SES, confirmed by the research mentioned above, have limited effects on outcomes of sepsis mortality and progression, but further research must be done [8] [37].

4.3. Awareness and Education for Patients and Healthcare Workers

Development and understanding of how sepsis works and knowledge of combating negative components of it can lead to more positive results between patients and healthcare workers. If it is understood that taking the proper dosage at the proper time can work as a preventative measure against antibiotic resistance, then it is more likely for those patients to avoid sepsis by implementing prospective scheduling that effectively reminds the patient to do so appropriately and accordingly [32]. Taking too many drug therapies will lead to poisoning, while too little will allow surviving microbes to transform and adapt to the conditions that make them resistant to that drug. Improper timing of consuming those drugs will amplify those situations. Moreover, preventative measures can be taken at the hospital by healthcare workers. Sanitary protocols should be carried out so that new pathogens are not introduced to the patient and that if any previous patient had multidrug resistant microbes, those areas should be isolated and dealt with accordingly to minimize spread. Ventilator usage should also be monitored, as they are susceptible to microbial contamination that may not have been cleaned properly [38]. In addition to these approaches, Breijyeh and his team suggest warning patients not to self-treat themselves and handing out pamphlets about antibiotic resistance to spread awareness. Self-treatment is dangerous because the lack of information about the drug can have unintended side effects that can even exacerbate diseases including sepsis. The power of prescription can ultimately affect how beneficial the treatment from the hospital will be [4]. Knowing what procedure to take to avoid sepsis can solve many of the problems regarding the misuse of drugs and hospital sanitary conditions.

4.4. Adverse Effects of Continued Antibiotic Administration to Antibiotic Resistant Patients

When patients are diagnosed with sepsis infection, physicians are recommended to administer broad spectrum antibiotic therapy to reduce symptoms and mortality rates. However, attention needs to be directed towards the implications of over-administering antibiotics to patients who may have antibiotic resistant pathogens as this therapy can increase their chances of mortality. The most common empiric antibiotics prescribed to sepsis patients include Vancomycin, levofloxacin, ciprofloxacin, piperacillin-tazobactam and ceftriaxone [18]. Many patients who do not need to take antibiotics are still administered this therapy, which is an increasing concern as empiric antibiotic therapy should only be administered to patients who suffer from sepsis shock. Those patients who are diagnosed with sepsis infection but did not suffer sepsis shock have a higher risk of mortality by taking antibiotics. Clostridioides difficile is a gram-positive bacterium that is the cause most implicated in antibiotic-associated diarrhea. The emergence of a newer hypervirulent strain North American pulsed-field gel electrophoresis type 1 (NAP1) has been attributed to the increase in incidence and severity of C. difficile infections (CDI) over the last decade [39]. Antibiotic use remains the leading risk factor for C. difficile infection. Several classes of antibiotics such as penicillins, cephalosporins, fluoroquinolone, and clindamycin are implicated in the disease's cause [40]. Many patients who are diagnosed with sepsis are not properly tested for antibiotic resistant pathogens in their blood samples. This results in inadequate treatment of patients who are resistant to the antibiotics that are administered to them. When antibiotic resistant patients are administered empiric antibiotics, the probability of survival decreases by a great amount [18]. Hence, further research needs to be done regarding adequate empiric antibiotic treatment for patients who truly require this therapy, by implementing stricter regimens for testing antibiotic resistant pathogens in the blood samples of sepsis diagnosed patients. Depending on blood culture results, treatment should be offered to sepsis patients accordingly rather than using broad spectrum empiric antibiotics. By not analyzing blood culture samples, this can lead to an increase in antibiotic resistance as a result of excessive administration of broad spectrum antibiotics. Genetic evaluation of sepsis patients should also be considered to understand whether genes play a role in the severity and morbidity of sepsis shock and infection, and whether there is a genetic component in pathogenic antibiotic resistance.

5. Conclusion

The studies point toward multiple factors that need to be taken into account when treating patients with sepsis. Firstly, the severity and disease morbidity needs to be evaluated before administering broad spectrum empiric antibiotics. This needs to be done in order to prevent the overuse of antibiotics in patients who did not suffer from sepsis shock, as the misuse of antibiotics can play a role in increased hospital mortality of sepsis patients. Sepsis patients need to be tested

for antibiotic resistant pathogens in their blood before the administration of empiric broad spectrum antibiotics. Furthermore, the timing of antibiotic administration and fluid resuscitation is crucial in preventing mortality from sepsis and it is recommended that antibiotics are administered promptly after sepsis diagnosis. Many people of low socioeconomic status may face hardships in accessing healthcare services and resources for sepsis treatment, creating a barrier that prevents them from being provided the best quality care when diagnosed with sepsis. In addition, increasing awareness of sepsis and the importance of timing in sepsis treatment through educational interventions can help alleviate misunderstanding toward the disease and prevent sepsis patients from not getting adequate care.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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