Clinical Management of Multidrug-Resistant Sepsis

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Sepsis is a critical medical condition associated with significant biological and chemical abnormalities that pose a high death rate. Unlike superficial and confined infections, sepsis is a complex disturbance of the delicate immunologic equilibrium between inflammatory and anti-inflammatory responses. This interaction demonstrates the fragile connection between the immune system and the clinical signs of sepsis. Sepsis globally accounts for an alarming annual toll of 48.9 million cases, resulting in 11 million deaths, and inflicts an economic burden of approximately USD 38 billion on the United States healthcare system. The rise of multidrug-resistant organisms (MDROs) has elevated the urgency surrounding the management of multidrug-resistant (MDR) sepsis, evolving into a critical global health concern.

Keywords: sepsis ; drug resistance ; microbial ; mortality ; antimicrobial ; organ dysfunction

1. Introduction

Sepsis is a critical medical condition associated with significant biological and chemical abnormalities that pose a high death rate. Unlike superficial and confined infections, sepsis is a complex disturbance of the delicate immunologic equilibrium between inflammatory and anti-inflammatory responses. This interaction demonstrates the fragile connection between the immune system and the clinical signs of sepsis. Over the past few decades, a comprehensive definition of “sepsis” has continuously evolved and improved [1]. Significantly, the current definition of sepsis (Sepsis-3) was proposed by the Third International Consensus, which defined it as “organ dysfunction caused by a dysregulated host response to infection.”. This description is the first to stress the vital function played by the natural and acquired immune system response at the onset of a medical illness [2].

During the initial stages of sepsis, the immune system mediates the activation of pro- and anti-inflammatory cytokines, pathogen-related molecules, and mediators, leading to the initiation of the complement cascade and coagulation [3]. For instance, numerous endogenous host-derived signals like damage-associated molecular patterns (DAMPs) or exogenous stimulations like pathogen-derived molecular patterns (PAMPs), such as DNA fragments, lipids, exotoxins, and endotoxins, are the starting signals for sepsis. These molecules interact with toll-like receptors (TLRs) present on the surface of antigen-presenting cells (APCs) and monocytes, leading to the expression of genes associated with pro-inflammatory interleukins (IL, IL-1, IL-6, IL-8, IL-12, and IL-18), tumor necrosis factor-alpha (TNF-α), and interferons (IFNs like IFN-y) and anti-inflammatory (IL-10) pathways and acquired immunity [4][5]; these processes are usually observed during the initial stages of sepsis [6][7][8]. This upregulated inflammation progresses to concomitant immunosuppression, leading to progressive tissue damage, multi-organ failure, increased immune cell apoptosis, and T cell exhaustion, which all together result in "immunoparalysis," thereby making sepsis patients prone to opportunistic and nosocomial infection [6][9]. A signal transduction caused by PAMPs- and DAMPs-mediated activation of monocytes and APCs causes the translocation of nuclear factor-kappa-light-chain-enhancer of activated B cells (NF-κB) into the cell nuclei. However, in short, the overall impact of the dysregulated immune response, whether hyper- or hypo-responsiveness, on the individual’s immunological response is highly personalized, leading to significant challenges in diagnosis [1].

Sepsis is a worldwide public health concern characterized by high rates of morbidity and mortality and a significant financial burden [10][11]. For instance, Rudd and coworkers recently revealed the alarming worldwide estimations of sepsis, as 48.9 million cases of sepsis were reported in 2017, with 11 million deaths attributable to sepsis [11]. In 2011, sepsis substantially burdened healthcare facilities in the United States with USD 20 billion in annual costs [12]. Additionally, numerous indirect expenses might dramatically impact the quality of life of patients with sepsis. For instance, older patients with sepsis may experience long-term severe health issues, such as cognitive impairment and functional disability [13]. Furthermore, a study on the sepsis burden in the Indian intensive care unit (ICU) revealed that the elderly population is more prone to sepsis due to multiple comorbidities caused by compromised immunity. The study found that 132 out of 387 patients with sepsis had septic shock, with the lungs (45.5%) being the most common site of infection. The mortality rate was 60.7% and 78.9% in old and very old patients, compared to a 45.6% mortality rate observed in younger adults

[14]. Similarly, another study identifying sepsis burden in Malaysian ICUs revealed that aging was significantly associated with a 30-day mortality rate among elderly sepsis patients (particularly patients aged ≥65 years), with a high 30-day mortality rate (28.9%) among elderly sepsis patients [15].

Like acute myocardial infarction and cerebrovascular stroke, sepsis is a critical and persistent chronological condition. In the case of sepsis, early and correct usage of antimicrobial drugs is of utmost significance within the first hour of detection, concurrently with organ support. If the microbial pathogen emerges as an MDR, including the methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), and MDR *Pseudomonas aeruginosa*, the therapeutic efficacy of currently available antimicrobial drugs is compromised, which hinders treatment success. Additionally, multidrug resistance poses a substantial risk of developing numerous sepsis-related adverse effects [16], necessitating prompt administration of the most appropriate antimicrobial therapy. However, while antibiotic resistance in bacteria is continuously growing globally, it poses a critical challenge to treating clinical infectious diseases, particularly those leading to life-threatening sepsis, septic shock, and multi-organ failure [17]. Additionally, as bacteria evolve, new mechanisms of resistance are emerging regularly and spreading worldwide, which are restricting current treatment options and making it challenging to treat prevalent infectious diseases [18]. Despite the persistent need for new antimicrobial drugs, major pharmaceutical industries have withdrawn from this field due to the rising costs of clinical trials, demanding approval criteria, and a general lack of economic viability [19][20]. This has widened the gap between the urgent public health need for effective antibiotics and the diminishing prospects of developing new antibacterial medications, resulting in a concerning situation [19].

Most patients with sepsis are given empirical antibiotic treatment without a prior confirmed diagnosis. This may raise the likelihood of developing multidrug resistance, accompanied by significant ecological adverse effects. Moreover, sepsis patients receive higher initial doses of empirical antimicrobial therapy regardless of organ failure, which may increase the synthesis of circulating pro-inflammatory and anti-inflammatory mediators, negatively impacting their overall health and well-being [21]. Additionally, the widespread misuse of antibiotics contributes significantly to increased mortality rates [22] and the surge in antimicrobial resistance (AMR). This misuse jeopardizes individual health and overburdens national healthcare systems financially [23]. One major contributor to antibiotic overuse is the unethical sale of antibiotics without proper prescriptions or diagnostic tests [24]. Similarly, self-medication practices often driven by economic constraints result in an incomplete antibiotic course, which promotes antibiotic resistance development due to suboptimal dosing [25]. Additionally, economic incentives for vendors to promote antibiotic sales make changing such practices challenging [26]. Furthermore, it is only now starting to understand the implications of antibiotic restrictions on outcomes and costs. It is hindered by the absence of universal ethical guidelines and comprehensive data on outcomes. Additionally, the concept of “best” and “effective” therapy varies significantly among groups, which makes the decision to select antibiotics difficult. Moreover, suboptimal antibiotic therapy cannot eradicate the infectious agent from the body, exposing affected individuals to the risk of adverse outcomes and wider antimicrobial resistance. Therefore, rational antibiotic usage primarily relies on identifying patients who, in fact, require treatment or optimizing treatment for a faster recovery [27].

2. Clinical Management of MDR Sepsis

Despite substantial advancements in the knowledge of the pathophysiology of sepsis, numerous clinical trials have been unsuccessful in identifying novel therapies that can alter the course of the disease [28][29]. Recognizing sepsis as a medical emergency is essential since, in the absence of definitive treatment, therapeutic interventions involve timely management of infection and organ support [30]. The 2016 Surviving Sepsis Campaign (SCC) guidelines strongly advise the prompt administration of intravenous broad-spectrum antibiotics, ideally within an hour following sepsis detection [31]. Several publications on sepsis and septic shock have found that delayed antibiotic administration is linked with adverse outcomes [32][33][34]. Beyond their apparent advantages, broad-spectrum antibiotics can cause substantial damage, such as antibiotic-associated adverse effects and potentially fatal AMR-related consequences [35][36]. Infections with MDRO have significantly increased worldwide, restricting the therapeutic options. The growing AMR is estimated to be responsible for approximately 10 million deaths each year by 2050. Therefore, treating patients with sepsis and septic shock by augmenting antimicrobial efficacy and avoiding the emergence of MDR strains is one of the primary concerns. Regarding this, antimicrobial stewardship (AS) is an important strategy for sepsis care since it focuses on multi-professional teamwork [for example, microbiologists, infectious disease specialists, and pharmacists] with appropriate, adequate, and optimized antimicrobial therapy [37].

Various studies have confirmed improved survival rates in sepsis patients with early and suitable antimicrobial administration and efficient source control [38], as validated by the inclusion of similar recommendations in 2016 SSC guidelines for early delivery of appropriate broad-spectrum antimicrobial drugs within one hour of hospital admission in patients afflicted by sepsis and septic shock [31][39]. Moreover, administering empiric antibiotic therapy directed at the most

likely pathogens involved in infectious sepsis is crucial to improving patient outcomes. Numerous published manuscripts have discussed the adverse impact and consequences of inadequate empiric therapy in sepsis patients [37][40][41][42][43][44]. Notably, prescribing ineffective empiric therapy is prevalent in ICUs, occurring in 10–40% of sepsis cases, which varies depending on the frequency of MDR pathogens [44][45]. Recent studies have found that the patient group with higher disease severity scores is most likely to benefit from appropriate antibiotic treatment. In contrast, ineffective empiric antimicrobial therapy was linked with a 5-fold decrease in the survival of over 5000 individuals suffering from septic shock [32]. Another prospective study has found a significantly increased mortality rate among patients with septic shock and an average of three organ dysfunctions [43]. An appropriate empiric antimicrobial therapy means prescribing drugs that cover almost all potential pathogens responsible for the suspected infection. To achieve this, certain pathogen- and patient-related factors must be considered [37][46], including weight, age, allergies, comorbidities, chronic organ dysfunction, immunosuppressive therapy, and previous antibiotic or infection history. The risk of MDR pathogens should also be considered, including lengthy hospital stays, previous hospital admissions, the presence of invasive medical devices, and prior encounters with MDR pathogens [37]. Several investigations into the detrimental consequences and outcomes of delayed antimicrobial provision in patients with sepsis have concluded similar results [47][48][49]. These studies have confirmed that appropriate antibiotic therapy significantly decreased the mortality rate when it was given within ≤1 h [50], whereas each hour of delay in the treatment increased mortality [51] and dropped the overall survival rate by an average of 7.6% [52]. Besides delayed antibiotic administration, lengthy hospital stays [49][53], acute renal [54] and lung [55] diseases, and worsening organ dysfunction [56] have also been found to be common factors associated with increased mortality in sepsis patients.

Compared to these findings, various studies were unsuccessful in determining the usefulness of timely antimicrobial therapy [57][58][59]. A meta-analysis comprising over 16,000 individuals with sepsis and septic shock from 11 studies identified an insignificant difference between antibiotic administration (within 3 h) and mortality rate [60]. Another meta-analysis study comprising 11 studies on sepsis patients identified a 33% reduction in mortality among patients receiving early empiric antibiotic therapy (≤1 h) compared to those with delayed antibiotic administration (>1 h) [61]. A recent systematic review concluded that the mortality rate significantly decreased in patients with septic shock receiving early and adequate empiric antibiotic therapy [42]. Despite inconsistent outcomes, there is substantial agreement among international specialists on the need for prompt antimicrobial therapy in patients suffering from sepsis and septic shock, and novel ideas have recently been offered. A “door-to-needle” duration of 60 min has been advocated for antibiotic delivery, which indicates global concerns about launching a time window for successful therapy after sepsis detection [35]. Nonetheless, ensuring a competent application of institutional standards for antibiotic administration within 1 h after presentation remains difficult.

Given the rapidly growing prevalence of MDR infections, combined antibiotic therapy is commonly advised to warrant a larger antimicrobial spectrum and appropriate empiric coverage. The combined therapy is described as using antibiotics from two separate classes that have activity against a single infection, primarily to speed pathogen elimination and increase the susceptibility of pathogens to treatment [62]. To ensure the likelihood of having at least one active antibiotic against the possible pathogen involved, the Infectious Diseases Society of America (IDSA) endorses using two active medicines against Gram-negative bacilli for empiric treatment of septic shock [63]. Recognizing the need to encourage antibiotic judiciousness, the IDSA formed a committee to explore suggestions for prudent antibiotic usage in treating sepsis. The experts accepted ten antibiotic class combinations out of a total of 21. Concerns about rising resistance and proper pathogen coverage were stated as factors for selecting such combinations. The use of any combination involving macrolides or ciprofloxacin and specific pairings of aztreonam with cephalosporins and aminoglycosides with intravenous clindamycin were prohibited [64].

Studies on combination therapy have yielded conflicting findings, and there is a scarcity of well-powered randomized controlled trials examining this particular issue. Numerous observational studies, however, demonstrated that combination therapy outperformed monotherapy in individuals suffering from sepsis and septic shock [65][66]. For instance, a meta-regression analysis found a link between combination therapy and a high survival rate among severely ill sepsis patients with a higher mortality risk. Unexpectedly, this meta-analysis identified higher mortality among the patient group with a low risk of death [67]. Similar findings were reported in other studies where researchers linked higher mortality with nephrotoxic side effects leading to renal failure [68]. Based on these inconsistent findings, some specialists advocate employing a pair of antibiotics for the initial treatment of patients with septic shock and suspected MDR pathogen infections. Even with negative culture results, treatment can be cut down to personalized therapy at the minimum acceptable time after microbiological isolation or a satisfactory clinical response [69]. To assess the effectiveness of different antibiotic combinations, well-powered randomized controlled trials examining multiple antibiotic combinations in different situations should be conducted [70]. Additionally, individualized therapies tailored to patients’ unique conditions, like diabetes, renal or hepatic failure, or immunosuppression, can yield favorable results instead of applying a uniform approach.

As organ dysfunction is a frequent complication of sepsis, supportive care and management of organ dysfunction are essential components of sepsis treatment to reduce complications and enhance patient outcomes. Hemodynamic support and mechanical ventilation are the two fundamental pillars of supportive care. Hemodynamic support entails maintaining proper tissue perfusion and oxygen supply, fluid resuscitation to restore blood pressure, and adequate organ perfusion. Vasopressor medications may also be required to treat refractory hypotension and to sustain cardiac output. Similar to this, sepsis patients with acute respiratory distress syndrome benefit from mechanical ventilation techniques such as low tidal volume ventilation and prone posture. Furthermore, renal and liver function should be constantly monitored to maintain optimal fluid and electrolyte balance and the fine balance of acids and bases. Some patients may need hemodialysis as a renal replacement therapy to prevent damage to other bodily organs caused by fluid imbalance and the presence of creatinine and urea in the blood, which hinder sepsis treatment [70][71][72].

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