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Review Article

Sepsis, Antimicrobial Resistance, and Alternative Therapies

Negeri Debela*, Solome Nekahiwot

Department of Medical Laboratory Science, College of Health Sciences, Arsi University, Asella, Ethiopia

Abstract

Sepsis, a life-threatening condition caused by the body's excessive response to an infection, has emerged as a global health menace. Around 20% of all global deaths are attributable to sepsis. Conversely, the presence of antimicrobial resistance (AMR) poses a significant peril to the health system. AMR constitutes an escalating pandemic that we must not disregard, as the absence of effective antibiotics would compromise the treatment of even commonplace bacterial infections. Therefore, the increasing prevalence of AMR further adds complexity to the management and outcomes of individuals with sepsis. AMR plays a contributory role in aggravating the consequences of sepsis, ranging from prolonged hospitalization to mortality. The World Health Organization (WHO) has prioritized AMR as a major concern necessitating immediate action to prevent dire consequences in the future. Though, One Health approach, infection prevention, rational use of antibiotics, strengthening surveillance systems, as well as research and development, are crucial strategies in combating antimicrobial resistance, alternative therapies, such as phage therapy and immunotherapeutics, are being explored for the management of AMR infections. Advances in these therapies show promise in addressing the challenges posed by antibiotic resistance in treating sepsis. In this critical assessment, we succinctly delineate the existing challenges of AMR in managing sepsis cases, and we provide an overview of the advancements in treating sepsis through alternative therapeutic modalities.

Keywords

Sepsis, Antimicrobial Resistance, Alternative Therapy, Phage Therapy, Immunotherapeutics

1. Introduction

Sepsis has emerged as a worldwide health menace, impacting a staggering 30 million individuals across the globe and leading to 11 million fatalities annually, comprising nearly 20% of the total global mortality [1]. Notably, sepsis stands as the leading cause of death in hospital environments, and has been identified as the predominant element attributable to the expenses of the healthcare system [2].

The recent sepsis definitions, the Third International Consensus Definitions (Sepsis-3) [3], has defined sepsis as a life-threatening malfunction of organs caused by an unregulated response of the host organism to infection. Septic shock, on the other hand, is defined as sepsis accompanied by circulatory, cellular, and metabolic dysfunction that is associated with a heightened risk of mortality [3, 4].

Sepsis is a widespread and impactful condition with significant global implications, in terms of morbidity and mortality [2]. The occurrence of sepsis is intricately influenced by a multifaceted interplay of factors involving the host,

*Corresponding author: negideb@gmail.com (Negeri Debela)

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pathogen, and the healthcare system. While various chronic diseases and immunodeficiency disorders contribute to an increased susceptibility to sepsis, certain populations, such as neonates, pregnant women, the elderly, individuals with serious coexisting conditions, and those in resource-limited settings, experience a disproportionately higher impact [5]. It is noteworthy that there is a direct correlation between the severity of sepsis and the rate of mortality [6].

Bacteria are predominantly responsible for initiating infections that can progress to sepsis [5]. The challenge in treating sepsis arises from the ability of these pathogens to thrive and proliferate despite antimicrobial drug interventions [7]. Initial antibiotic treatment during the first 1-2 days is typically empirical, and the consensus is that evidence-based antibiotic therapy contributes to reduced mortality [8]. As a result, healthcare providers seek to provide optimal empirical antimicrobial treatment for hospitalized patients with sepsis, often at the expense of administering superfluous antibiotics [9]. This practice has been associated with the emergence of AMR.

AMR is an enduring phenomenon that arises from the interactions between organisms and their surrounding milieu. Given that a substantial majority of antibiotics have been naturally produced by bacteria and fungi over the course of millions of years, microorganisms have evolved mechanisms to withstand the impact of these agents, flourish, and proliferate [10]. Consequently, many bacteria are naturally resistant to one or even a majority of antibiotics, and that resistance may be shared among bacteria by horizontal gene transfer or external genetic acquisition from the environment [11, 12].

AMR poses a significant obstacle in the treatment of sepsis and has emerged as a prominent public health menace in the 21st century. The World Health Organization (WHO) has accorded priority to AMR as one of the foremost ten global public health threats confronting mankind, necessitating immediate attention. Failure to address this crucial concern will render several bacterial pathogens highly lethal in the imminent future [13].

2. The Burden of Antimicrobial Resistance

The implications of AMR are far-reaching in terms of the environment, health, and finances. The issue of antibiotic resistance emerged after the discovery of the first antibiotic, Penicillin, in 1928, with reports of resistance to Penicillin dating back to as early as 1940. Alexander Fleming, upon receiving the Nobel Prize in 1945 for his discovery of penicillin and its efficacy in treating various infectious diseases, was already cognizant of the potential fragility of this powerful medical tool [12]. Even after 80 years, antimicrobials continue to play a vital role in the success of both human and veterinary medicine. However, there is an escalating number of bacterial pathogens that are exhibiting reduced susceptibility or complete resistance to antibiotics.

The bacteria species that currently pose the most significant risk to the effectiveness of antibiotics are Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter faecium [14]. These bacteria, collectively referred to as the ESKAPE pathogens, are highly infectious, fatal, and responsible for the rising prevalence of AMR infections. The development of alternative treatments for ESKAPE pathogens is a global priority [15].

The first comprehensive estimation of the global burden of AMR across 204 different nations was documented in 2019. The findings affirm that bacterial AMR is the primary cause of mortality and disability on a global scale, surpassing both HIV/AIDS and malaria in terms of its burden [16]. AMR leads to significant escalations in healthcare expenditures, and this burden remains inadequately quantified at the global level. It has been approximated that 'sepsis' results in 40–60 million cases and accounts for one in every five fatalities annually [1]. AMR presents a substantial obstacle in the management of sepsis, as it escalates the global incidence of sepsis and at least doubles the risk of death [17]. Furthermore, if current trends persist, AMR will become the most prominent contributor to human mortality [1]. If AMR is permitted to proliferate unchecked, it will result in an additional 10 million lives lost each year by 2050, with a cumulative cost of US$100 trillion, exceeding the annual world GDP of today by one and a half times [18].

The WHO come to the understanding that the propagation of AMR is an exigent matter that necessitates a comprehensive and synchronized action plan on a global scale for mitigation. Failure to reverse the AMR will result in an alarming surge in mortality rates in the forthcoming years. Approximately 50% of sepsis cases are attributable to bacteria that exhibit resistance [19]. Recognizing the gravity of the situation, the WHO has given AMR a high-priority status as one of the paramount threats to public health worldwide [20]. In 2016, the High-Level Meeting of the United Nations General Assembly on Antimicrobial Resistance officially underscored the significance of addressing AMR and implored nations to commit to their respective AMR National Action Plans [21]. Despite these concerted endeavors, in 2019, the global burden of AMR associated with drug-resistant infections resulted in approximately 4.95 million fatalities. Of these fatalities, 1.27 million were exclusively caused by drug resistance. Furthermore, following ischemic heart disease and stroke, AMR emerged as the leading cause of death in 2019 [22]. Contrary to the prevalent notion that high-resource settings with greater antibiotic consumption would bear the brunt of the burden, it is noteworthy that some low- and middle-income countries (LMICs) exhibited the highest rates of AMR-related mortality. Indeed, AMR is progressively manifesting as a more severe predicament for several of the world's most impoverished nations. Sub-Saharan Africa

and South Asia, in particular, experienced the highest AMR-related death rates, directly correlating with the prevalence of resistance in these respective regions [16, 23].

In Ethiopia, there was a documented total of 21,200 fatalities that can be directly attributed to AMR, while an additional 85,300 deaths were found to be associated with AMR. The mortality rate caused by AMR in Ethiopia exceeds the mortality rates resulting from maternal and neonatal disorders, cardiovascular diseases, respiratory infections, enteric infections, and neoplasms [23].

The rise of resistance to infectious agents that pose a threat to public health is being driven by a combination of various factors. These factors encompass the negligent prescribing practices of healthcare professionals in relation to broad-spectrum antibiotics, the failure to comply with the recommended duration of treatment, and the imprudent use of antimicrobial agents by the general public. As a result, the resulting strains that are resistant to treatment spread among a larger population [24]. In Africa, and many other LMICs, inadequate antibiotic policies in conjunction with insufficient surveillance of antibiotic resistance result in the accumulation of antibiotic resistance, which contributes to the global reservoir of challenging-to-treat infections [25]. While AMR is a concern for both developed and developing countries, African countries are regarded as one of the epicenters of this issue for several reasons. Africa bears a significant burden of infectious diseases, and the treatment of infections is often mismanaged due to various factors, such as the absence of adequate diagnostic support in terms of quality and accessibility, the lack of reports on outbreaks, the persistence of outdated prescription practices among doctors, and various socioeconomic factors [24].

Furthermore, the current status of the clinical pipeline for innovative antimicrobial drugs demonstrates a lack of advancement. According to the WHO, a total of 32 antibiotics were reported to be in clinical development in 2019, specifically targeting the WHO's list of prioritized pathogens. Nevertheless, only six of these pharmaceuticals can be deemed ground-breaking or pioneering. Furthermore, the persistent issue of insufficient access to high-quality antimicrobial medications continues to present a significant challenge for countries at all levels of development [26]. This occurrence has emerged as a prominent threat to public health in the 21st century.

3. The Therapeutic Management of Sepsis

The management of sepsis entails the utilization of antimicrobial agents alongside intravenous fluids and medications targeted at alleviating symptoms. Nonetheless, the rise of bacterial AMR, a growing menace to public health, is rendering the application of antibiotics ineffective in combating numerous prevalent bacterial illnesses that impact both animals and humans [18].

The initial step in managing sepsis involves the identification of patients with sepsis. However, this task poses a challenge due to the subjective nature of sepsis diagnosis, particularly in the early stages of clinical presentation where symptoms are nonspecific and laboratory findings are still pending. Despite advancements in diagnostic techniques, it is important to note that only a relatively small percentage, approximately 30–40%, of patients suspected of having an infection actually receive a positive microbiological diagnosis [27]. Recent reports have highlighted cases where individuals have unfortunately perished because of their conditions lacking timely treatment [28]. This has led to a heightened emphasis on the prompt detection and management of suspected sepsis cases. Nevertheless, given the pending status of laboratory results and their limited sensitivity, healthcare practitioners are compelled to take action before the completion of investigative procedures. Though most experienced clinicians express confidence in applying sepsis definitions, only a minority have successfully identified cases of sepsis [29].

The effective management of sepsis necessitates not only addressing the underlying infection but also implementing life-saving medical interventions for vital organs [30, 31]. Research studies have demonstrated the clear advantage of promptly administering antimicrobials essential for eliminating the microorganisms responsible for sepsis [32]. Empirical antibiotic therapy must also take into account the site of infection, the common pathogen causing sepsis, and antibiotic sensitivity based on local patterns of antibiotic resistance [32]. Failure to identify the source of infection has the potential to result in mis-identification of the pathogen and inappropriate selection of antibiotics [33]. The global rise in AMR bacteria is increasingly compromising the effectiveness of antimicrobial therapy, especially in terms of empirically selecting appropriate antimicrobials [34]. The judicious use of empirical antibiotics is crucial in reducing the mortality rate of sepsis, and although the exact timing required is not fully understood, every effort should be made to administer such medications as quickly as possible, ideally within one hour of admission [35, 36].

Broad-spectrum antibiotics may be administered to critically ill patients in order to prevent the improper use of antibiotics, which could potentially be fatal [37]. The adjustment of the initial therapy to a broad-spectrum approach is necessary and should be based on the patient's clinical condition, the results of the microbial culture, and the susceptibility test for antibiotics. The modification of the initial antibiotic regimen should involve reducing the quantity and/or range of antibiotics. Additionally, in patients with uncomplicated infections who show signs of clinical improvement, the duration of therapy can be shortened, or in cases where a non-infectious cause has been identified for the patient's signs and symptoms, antibiotics can be discontinued altogether [38]. The prolonged use of broad-spectrum antibiotics can

result in the development of antibiotic resistance. Therefore, it is crucial to have knowledge of the local pathogen pattern based on the site of infection and microbial sensitivity in order to minimize the use of broad-spectrum antibiotics and the inappropriate use of empirical antibiotics.

Before administering antibiotics, it is imperative that blood cultures are obtained. The crucial aspect of this is the capacity to identify and characterize the antibiotic sensitivities of the cultured pathogens, which is essential for further management.

4. Impact of Antimicrobial Resistance on Sepsis

Antibiotics, which have proven to be highly efficacious interventions in the annals of medical practice, have been instrumental in preserving the lives of countless individuals [39]. The utilization of antibiotics has been extended to encompass a wide range of medical conditions; thus, it would be catastrophic if the efficacy of antibiotics in the realm of medicine were to be compromised or diminished. Regrettably, we find ourselves rapidly approaching such a dire era, commonly referred to as the "post-antibiotic era" [40]. Because sepsis is a significant driver of antibiotic use, and infections caused by drug-resistant pathogens can lead to sepsis.

The precise and timely identification of sepsis is of utmost importance in determining the medications that are most likely to be effective in combating the underlying infection and hindering its development into sepsis. To achieve this, medical professionals employ a jigsaw approach, utilizing clinical characteristics, inflammatory markers, and microbiological analysis [23]. In the context of uncertainty, clinicians must act, weighing up the risks of failing to treat sepsis against over-diagnosis, over-treatment, and the associated risk of increasing AMR. However, patients whose organ dysfunction is secondary to a cause other than infection will still potentially be misdiagnosed and unnecessary antimicrobials administered, which may contribute to the AMR emergence.

AMR plays a central role in determining the clinical unresponsiveness to treatment and the rapid progression of infection to sepsis and septic shock. Sepsis patients infected with resistant pathogens have been observed to be at an increased risk of death [41]. Research conducted across the globe has revealed escalating levels of resistance to multiple drugs, which is concerning for the future [42, 43]. Due to the growing resistance of microorganisms to antimicrobial medications used for treating infections, individuals are becoming more susceptible to the development of sepsis. In the majority of cases, sepsis represents a grave complication of an infection, and unless promptly identified and addressed, it can progress to septic shock, multiple organ failure, and ultimately, demise [44].

Broadly speaking, infections resulting from resistant bacterial strains lead to adverse outcomes that are up to twice as high in comparison to infections from normal strains [9]. These adverse outcomes can manifest both clinically and economically and are indicative of the ineffectiveness of antibiotic treatment in curing infections. It is the cost associated with these treatment failures, both for patients and the healthcare system, that underlies the negative impact of antibiotic resistance [45]. A discrepancy between the actual therapeutic agent and the ensuing susceptibility findings for a specific organism is among the most noteworthy aspects that hinder the promptness of effective treatment [46]. Moreover, the manifestation of resistance during therapy has also been substantiated to exert a negative and significant impact on outcomes [47].

Powerful antibiotics with a broad-spectrum can treat a range of infections and are particularly valuable when clinicians are uncertain about the exact cause. In an effort to surmount the intricate intricacies associated with this matter, anyone entering a hospital with clinical features is flagged as having sepsis and should be prescribed broad-spectrum antibiotics within an hour [48]. But this “better safe than sorry” approach can have unintended ramifications of AMR [49]. The possible differential diagnoses of such clinical features in certain patients would render the antibiotics unnecessary. It is worth noting that in around 40% of patients, the pathogen is not identified and treatment is not de-escalated [50].

5. Alternative Therapies for Sepsis Management

AMR is one of the biggest threats to global health, as it can make the treatment of bacterial infections in humans difficult owing to their high incidence rate, mortality, and treatment costs. In general, the report divulges the present challenges associated with AMR and the pressing need to discover novel, efficacious antimicrobial treatments [51]. Given that numerous pharmaceutical corporations no longer engage in the creation of new antibiotics, satisfying the urgent demand for fresh therapeutic agents against AMR proves to be challenging. Alternative therapeutic modalities, such as phage therapy and immunotherapeutics for the management of diverse AMR infections, are currently undergoing clinical development.

Phage therapy

Phages, short for "bacteriophages" symbolizing their capacity to eliminate bacteria, were discovered by Frederick Twort in the year 1915. The evaluation of the antimicrobial characteristics of the bacteriophages was carried out by Professor Twort's team at an early stage. Unfortunately, the failure in the clinical realm that followed can be ascribed to the enigmatic mechanisms of action that were not thoroughly comprehended [52]. Bacteriophages, which were unveiled before the advent of antibiotics, have once again been em-

braced as a prospective remedy to counter antimicrobial resistance.

While the utilization of bacteriophage therapy as a treatment strategy is not a novel concept, it appears to instill a sense of recurring optimism in the battle against AMR. A century ago, the initial documentation regarding the effectiveness of bacteriophage therapy garnered significant attention [53]. Regrettably, interest in bacteriophage-based therapies waned following World War II due to the emergence of antibiotics, subsequently entering a phase of stagnation. However, in the current era marked by the escalating crisis of bacterial resistance, bacteriophage therapy has experienced a global resurgence. There was a proposal put forth by scholars hailing from academic institutions and industries to identify potential therapeutic alternatives to antibiotics. Notably, bacteriophage therapy secured a place among the top ten strategies deemed noteworthy by this collective [54].

Bacteriophages are omnipresent and represent the most prevalent organisms on our planet, with an estimated 10^{31} phage particles at any given time [55]. Studies on bacteriophage therapy in animal models have revealed that bacteriophage therapy may diminish the density of the infected AMR bacterial population [56, 57] and has also proven advantageous in the treatment of pneumonia caused by resistant bacteria [58, 59].

There was the successful treatment of a patient with sepsis caused by Pseudomonas aeruginosa using phages. Following intravenous treatment, blood cultures promptly became negative, C-reactive protein levels decreased, fever resolved, and renal function recovered [60]. A different study with a striking result in another individual with sepsis triggered by *Acinetobacter baumannii*, in which the introduction of bacteriophages via intravenous and percutaneous routes into localized collections of pus led to the prompt eradication of the infection, reversal of the patient's declining medical status [61]. Conversely, the use of bacteriophages as adjunct therapy appears to be safe in critically ill patients and effective as a "rescue" treatment when expected mortality is so high [62]. A recent report concludes that phage therapy in sepsis treatment can be anticipated in the near future [3]. However, we still know much less about how to use phages. If we are to continue with the therapeutic use of phages, we must make all efforts.

Immunotherapeutics

During sepsis, the reaction of the host organism can be modified in various manners, thereby accounting for the highly diverse clinical manifestation, treatment responses, and prognosis [63]. Although it has long been believed that sepsis primarily arises from an excessive immune response to an infection, it is now recognized that a secondary immunosuppressive reaction often arises concurrently [64-66]. The manipulation of the immune response to combat infection holds great promise as a treatment approach for sepsis. Immunotherapy, as a means to manage sepsis, centers on the modulation of the immune response to prevent the deleterious consequences of inflammation while still maintaining its advantageous effects on pathogen clearance. Several strategies are being investigated in this field, including the use of immunomodulation agents, cell-based therapies, and immune checkpoint inhibitors.

Interferon gamma (IFN-γ)

IFN-γ represents a highly promising class of immunomodulating agents that serve to augment the immune response of the host, stimulate immune cell phagocytic function, and facilitate the elimination of bacterial pathogens. T helper 1 cells are the predominant producers of IFN-γ, which in turn activate macrophages and bolster the immune response against invading pathogens [67]. In the context of septic patients, the secretion of IFN-γ is compromised in peripheral blood mononuclear cells (PBMCs) upon ex vivo stimulation, as compared to healthy controls [68]. Furthermore, PBMCs derived from patients who developed secondary infections or experienced fatal outcomes exhibited markedly reduced IFN-γ secretion in comparison to immune cells from individuals who achieved recovery. Notably, the administration of IFN-γ treatment has been observed to heighten HLA-DR expression and enhance TNF production in response to lipopolysaccharide (LPS) in monocytes of septic patients [69]. Pre-clinical investigations have demonstrated that IFN-γ treatment effectively reduces mortality rates and improves clinical outcomes in animal models of sepsis. In the clinical setting, IFN-γ has been employed to treat infections in immunosuppressed patients afflicted with chronic granulomatous disease and hematological cancers [70, 71]. Studies focusing on patients with fungal sepsis have revealed that IFN-γ treatment serves to reinstate HLA-DR expression and enhance the capacity of leukocytes to produce pro-inflammatory cytokines [72]. Nonetheless, clinical trials involving human subjects have not consistently yielded conclusive results, thereby necessitating further research to ascertain its potential benefits.

Mesenchymal stem cells (MSCs)

Animal investigations have illustrated that MSCs have a favorable impact on survival rates and organ dysfunction in septic models. This is achieved through the enhancement of bacterial clearance, modulation of the immune response, limitation of apoptosis, and promotion of injury repair [72]. MSCs exhibit antibacterial effects by means of enhancing macrophage endocytosis and the secretion of antimicrobial peptides [72]. Additionally, MSCs demonstrate anti-inflammatory properties by restricting the activation of NLRP3-inflammasome/caspase-1 and the production of pro-inflammatory cytokines, including TNF and IL-6. Moreover, MSCs promote the development of regulatory T cells (Tregs), thereby enhancing injury repair and limiting excessive inflammation [73]. Recently, a clinical experiment that involved the administration of MSCs to septic shock-afflicted patients demonstrated the absence of any apprehensions regarding safety [74]. In the aforementioned investigation, no disparities pertaining to the reaction of pro-inflammatory

cytokines were discerned between those treated with MSCs and those treated conventionally. At present, multiple ongoing clinical trials are actively exploring the safety and effectiveness of MSCs in patients suffering from sepsis.

Immune checkpoint inhibitors

Immune checkpoint inhibitors, primarily utilized in the context of cancer treatment, have demonstrated potential in the management of sepsis. These inhibitors selectively target molecules responsible for regulating the immune response and enhancing the function of T cells [75]. Immune checkpoint receptors activate inhibitory pathways that are crucial for maintaining self-tolerance and regulating ongoing immune responses. The mechanism of action of checkpoint inhibitors involves the prevention of the apoptotic or senescent death of activated T cells. Both pre-clinical and clinical studies have revealed that several checkpoint receptors, including PD-1, and CTLA-4, as well as their corresponding ligands, are upregulated during sepsis [76]. Notably, increased expression levels of PD-1 and PD-1L have been observed on monocytes and CD4+ lymphocytes in patients with septic shock compared to healthy individuals [77, 78]. It is worth mentioning that heightened expression of these receptors has been associated with a higher incidence of nosocomial infections and mortality. Treatment with anti-PD-1 and anti-PD-L1 antibodies has been shown to inhibit apoptosis, reverse immune dysfunction, and improve survival in murine sepsis models [79]. An ex vivo study demonstrated that blocking the PD-1/PD-L1 pathway in PBMCs obtained from septic patients increased the production of key cytokines and prevented apoptotic cell death [80]). A case study involving an immunosuppressed patient with therapy-refractory fungal sepsis reported that combined treatment with anti-PD-1 antibodies and IFN-γ increased the number of lymphocytes and monocytic HLA-DR expression [81]. Importantly, a monoclonal antibody targeting PD-1 was shown to be well tolerated in immunocompromised patients with sepsis in a randomized clinical trial [82].

6. Stop Sepsis: by Addressing AMR

AMR has emerged as a significant global challenge within the realm of modern medicine, impacting both human and animal populations. Nevertheless, efforts are being implemented to confront this crisis, though insufficiently addressed on a global scale. The worldwide prevalence of AMR exhibits no indications of diminishing; instead, it exacerbates the strain on human and veterinary medicine. Analogous to the phenomenon of global warming, AMR represents an ecological catastrophe of immeasurable proportions and lacks any discernible solution.

Strengthening the One Health approach

The interconnectedness of human, animal, and environmental health is undeniable. Frequently, both animals and humans fall victim to the same disease-causing agents and are administered identical antibiotics, thereby exerting a mutual influence on the issue of antibiotic resistance. Thus, it is imperative to adopt a comprehensive strategy, known as the One Health approach, in order to effectively address the emergence of antimicrobial resistance. All sectors must collaborate closely to safeguard the well-being of both individuals and animals, as well as to uphold the efficacy of antibiotic treatments [83].

The WHO has explicitly advocated for more stringent legislation in order to minimize the use of antimicrobials in animals. To reduce antimicrobial usage in animals, it is possible to implement measures such as improved sanitation, the inclusion of probiotics or nutritional supplements in animal feed, as well as vaccination against common animal diseases [84]. It is crucial to establish a connection between public health, healthcare, animal health, and the agricultural sector, and this connection must be enhanced across all areas and levels. The development of national action plans to combat AMR, for instance, necessitates cooperation among stakeholders from various relevant sectors. Furthermore, research associations should unite scientists from different fields by conducting studies on AMR in humans, animals, food, and the environment. A comprehensive, global approach is the only means by which a lasting change in the situation can be achieved.

Infection prevention

Infection prevention and control (IPC) is a practical, evidence-based approach preventing patients and health workers from being harmed by avoidable infections [85]. The understanding of AMR and infection prevention and control shall include the general populace, not only healthcare professionals. The measures implemented for infection prevention and control are specifically devised to minimize the transmission of pathogens, including those that have developed resistance, within healthcare facilities as well as in the broader community. This proactive approach serves to stop the proliferation of AMR pathogens [86].

There exists a comprehensive array of interventions that aid in the prevention and management of infections as well as the dissemination of bacteria that are resistant to antimicrobial agents. The utilization of alcohol-based hand sanitizers or the act of washing hands has demonstrated its effectiveness in the prevention of infections [87]. This particular factor possesses the capability to impede the spread of infection and, consequently, the emergence of AMR. The current need necessitates a willingness to adhere to stringent standards of hygiene. These measures ought to be accompanied by the formulation and implementation of guidelines and training programs designed for healthcare professionals. The establishment of networks that encompass hospitals, ambulatory care facilities, nursing homes, laboratories, and public health institutions plays a vital role in facilitating the implementation of interventions within all sectors of healthcare [88].

Rational use of antibiotics

Committing to the utilization of antibiotics solely for ther-

apeutic purposes subsequent to individual diagnosis, and under the guidance of healthcare professionals in adherence with legislation. The irrational utilization of pharmaceuticals is a grave global predicament. In developing nations, at the primary level, fewer than 40% of patients in the public sector and fewer than 30% of patients in the private sector are managed in accordance with established treatment protocols [89]. Both the overarching reduction of antibiotic consumption and the abatement of inappropriate antibiotic utilization are indispensable measures to mitigate the emergence of resistant bacteria [89, 90].

Studies have demonstrated that there is a rising trend in the global utilization of antibiotics in the field of human medicine, even though there is still a prevalent issue of the inappropriate prescription of antibiotics. It has been approximated that a substantial portion, up to 50%, of all prescribed antimicrobial in healthcare facilities are unsuitable [83, 91]. In addition to the potential risks it poses to individual patients, the misuse of antibiotics is correlated with the escalation of pathogens' resistance to these antimicrobial agents. To address these concerns, Antibiotic Stewardship (ABS) programs have emerged with the aim of promoting the proper utilization of antibiotics in both human and animal settings [92]. By providing evidence-based recommendations and guidelines for the diagnosis and treatment of infections, ABS programs strive to enhance patient outcomes and hinder the progression of antibiotic resistance.

Strengthening the surveillance system

The AMR Surveillance program facilitates the dissemination of information regarding both existing and emerging patterns of AMR and antibiotic utilization in medical, veterinary, and agricultural contexts [87]. This program aims to address gaps in knowledge and develop effective strategies for combating antimicrobial resistance. Moreover, it is an invaluable tool that generates data on antimicrobial utilization and resistance, which is crucial for updating Essential Drug Lists (EDLs) as well as formulating policies for infection control. Additionally, it has the potential to enhance antimicrobial prescribing practices and contribute to the development of empirical therapy and standard treatment guidelines [93].

Surveillance systems have been implemented in numerous industrialized countries, monitoring antibiotic use, nosocomial infections, and animal health. The data show the dimension of the problem with detailed information obtained by national reference centers, permitting early detection of resistant strains that might pose a threat to public health and timely interventions. Strengthening these surveillance systems and enabling them to provide timely, accurate, representative, and comparable data are major steps in combating AMR [94].

Research and development (R&D)

The potential danger posed by AMR could potentially be diminished if there were universal capability in diagnosing human and animal diseases accurately if existing treatments were readily available and correctly utilized, and if the development of new treatments specifically targeted priority diseases that are at risk of resistance. Conducting research will continue to be a crucial strategy in combating the dissemination and impact of antimicrobial resistance [95]. AMR poses a worldwide challenge, and, therefore, research endeavors should be carried out on an international scale. Encouraging collaboration among international research groups in the field of AMR will enhance synergies and prevent redundant research efforts. Furthermore, it is imperative to foster interdisciplinary cooperation between human and veterinary medicine. The advancement of innovative antimicrobial drugs or alternatives is of equal importance to research aimed at gaining a better understanding of the emergence and transmission of resistance among different species [17].

The escalating global challenge of antibiotic resistance demands innovative solutions, and the WHO is at the forefront of efforts to address this critical issue. Through its leadership, the WHO is actively shaping the research and development agenda for novel antibacterial treatments, encompassing drugs, diagnostic tools, and pioneering approaches. Furthermore, the organization's collaborative engagement with diverse stakeholders underscores its commitment to promoting responsible usage of new products while ensuring widespread accessibility. By driving these initiatives, the WHO plays a pivotal role in the collective endeavor to combat AMR and safeguard public health on a global scale [96].

7. Conclusion

AMR has emerged as a significant obstacle in the treatment of sepsis and is a global public health threat. We should strive to enhance our understanding of the magnitude of the issue of AMR. Thorough and reliable data collection is imperative in the regulation of AMR. Regulations should be enforced, with rigorous monitoring of antibiotic usage as part of the policy. A global and interdisciplinary perspective must be taken into account in the development of new screening and diagnostic tools. The ecological and environmental aspects of the issue should not be overlooked; all components of the "one health" approach should be integral to the control policy. The present global interest indicates that AMR is no longer a disregarded matter. However, this attention alone is insufficient to combat AMR. A global code of conduct that incorporates all possible actions against AMR may eradicate AMR in the future. Non-antibiotic alternatives modalities, such as phage therapy and immunotherapeutics, are currently undergoing clinical development as possible solutions to AMR. Addressing AMR requires a comprehensive and synchronized action plan on a global scale, including measures to strengthen the One Health approach, combat and prevent infections, promote the rational use of antibiotics, strengthen the surveillance system, and strengthen research and development.

Abbreviations

AMR: Antimicrobial Resistance
WHO: World Health Organization
LMICs: Low- and Middle-Income Countries
PBMCs: Peripheral Blood Mononuclear Cells
MSCs: Mesenchymal Stem Cells
IPC: Infection Prevention and Control

Conflicts of Interest

The authors declare no conflicts of interest.

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