RESPIRATORY INFECTION AND ANTIMICROBIAL RESISTANCE

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ABSTRACT

Antimicrobial resistance to the effects of antibiotics has caused a significant public health problem with reduced effectiveness of standard treatments. Resistance occurs through various mechanisms such as genetic mutations, horizontal gene transfer, and selective pressure from the widespread use of antimicrobials. Antibiotic resistance requires genomic insights, new technologies, and innovative solutions. In the treatment of respiratory infections, mainly caused by *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus piogenes* and *Moraxella catarralis*, inappropriate use of antibiotics leads to the development of resistant bacteria. Pathogens can develop different specific mechanisms to avoid the effect of the antibiotic. Continuous therapeutic treatments with the same antibiotics can induce resistance, and therefore, research for developing new antibiotics is necessary to address pathogen resistance and ensure effective treatment.

KEYWORDS: *infection, antimicrobial resistance, microorganism, bacteria, antibiotic*

INTRODUCTION

Antimicrobial resistance refers to the ability of microorganisms, such as bacteria, viruses, fungi, and parasites, to withstand the effects of medications that once effectively treated them. This phenomenon is a significant public health concern as it leads to the reduced efficacy of standard treatments, prolonged illnesses, increased mortality, and the need for more potent and potentially toxic medications. Resistance arises through various mechanisms, including genetic mutations, horizontal gene transfer, and selective pressure from the widespread use of antimicrobials. Understanding and addressing pathogen resistance is critical for maintaining the effectiveness of current treatments and for the development of new therapeutic strategies.

Antimicrobial resistance is a dynamic and evolving challenge in modern medicine (1,2). Recent advancements and emerging trends highlight the complexity of this issue and the need for innovative solutions. Several new methods to combat resistance that are gaining attention in the scientific community include genomic insights and clustered regularly interspaced short palindromic repeats (CRISPR) technology, antibiotic stewardship programs, phage therapy, antimicrobial peptides (AMPs) and novel compounds, microbiome modulation, and global surveillance and big data (3-7).

DISCUSSION

The inappropriate use of antibiotics for treating respiratory infections, in which they are not necessarily required leads to the development of resistant bacterial strains, as well as unnecessarily exposing the patient to the adverse reactions of the pharmacological treatment and leading to a waste of economic resources. The most common etiological agents in bacterial respiratory infections are *Streptococcus pneumoniae, Haemophilus influenzae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Streptococcus piogenes*, and *Moraxella catarrhalis*.

S. pneumoniae is a gram-positive bacterium and a leading cause of pneumonia, meningitis, otitis media, and bacteremia, particularly in children and the elderly (8). It is encapsulated, which helps it evade the host's immune system. *S. pneumoniae* has developed resistance primarily through alterations in penicillin-binding proteins (PBPs), reducing the efficacy of beta-lactam antibiotics (9). Additionally, resistance to macrolides occurs via modification of the ribosomal target site or efflux mechanisms that expel the antibiotic from the bacterial cell (10). The emergence of multi-drug-resistant strains complicates treatment and highlights the need for ongoing surveillance and development of new antibiotics or vaccines (11).

Numerous studies have been conducted on the distribution of resistance of *S. pneumoniae*, the most common etiological agent of community-acquired pneumonia (CAP), to the most widely used antibiotics (beta-lactams and macrolides) (12-14). Pneumococci are germs that are highly sensitive to penicillin, both the natural versions, such as penicillin G, and the semi-synthetic versions, such as aminopenicillins (amoxocillin), with a minimum inhibitory concentration (MIC) of 0.01 μm/ml and 0.03 μm/ml respectively. However, the chemo-sensitivity of pneumococci to beta-lactams has undergone a notable change over the years due to the development of new local resistance (15).

Penicillin was produced in 1940 and was the first antibiotic used in infectious diseases (16), but penicillin-resistant strains of *S. pneumoniae* already appeared in 1970 with structural modifications of the PBPs of the bacterium preventing inhibition by the antibiotic of bacterial peptidoglycan synthesis (17). Macrolides were therefore used to treat pneumococcal infections. However, the frequent use of these drugs led to the appearance of *S. pneumoniae* species that were also resistant to macrolides.

The most common mechanisms of macrolide resistance are ribosomal methylation mediated by the erm(B) gene and efflux pump synthesis mediated by the mef(A) gene (18). Penicillum-resistant *S. pneumoniae* strains can be distinguished into intermediate-resistant strains and highly resistant strains based on MICs (19). The Clinical and Laboratory Standard Institute (CLSI) has defined the MIC breakpoints, for example, the threshold concentrations (micrograms per milliliter) to express the sensitivity and resistance of microorganisms to penicillin (20). Values between 0.12 and 1 μg/ml indicate intermediate resistance. Values greater than 2 μg/ml indicate high resistance.

Penicillin resistance has been on the increase over recent years, with distribution that varies considerably in different geographical areas. *S. pneumococcus* resistance to penicillin can reach approximately 44% in some regions of the United States (21,22), 22% in Brazil (23), as much as 70% in some European countries such as Spain, Hungary, and France (24,25), and levels as high as 70-78% in Asian countries such as South Korea, Hong Kong, and Taiwan (26,27).

In cases of respiratory infections caused by penicillin-resistant *S. pneumoniae* strains, high-dose amoxocillin clavulanate of 80-90 mg/kg per day should be administered, thus achieving antibiotic sensitivity rates of 99%. The MIC breakpoints used to distinguish macrolide-resistant *S. pneumoniae* strains are 1 μg/ml for azithromycin and 0.5 μg/ml for erythromycin (28). Erythromycin-resistant strains are particularly high in South America, Europe, South Africa, and Asia, and high numbers of azithromycin-resistant strains have been seen in North America and Saudi Arabia. In cases of resistance to macrolides, a third-generation cephalosporin is recommended and, as a second choice, one of the most recent antibiotics: fluoroquinolones (levofloxacin, moxifloxacin, etc.), ketolides (telithromycin), and oxazilodones (linezolide). Resistance to new-generation antibiotics is very low or absent (29).

H. influenzae is a gram-negative bacterium that can cause a range of infections, including respiratory tract infections, meningitis, and septicemia (30). It is especially known for causing serious infections in children before the advent of the *Haemophilus influenzae* serotype b (Hib) vaccine (31). *H. influenzae* has developed resistance through the production of beta-lactamase enzymes that degrade beta-lactam antibiotics, rendering them ineffective (32). Some strains have also acquired mutations in penicillin-binding proteins, contributing to beta-lactam resistance (33). Resistance to other antibiotics, such as macrolides and tetracyclines, often arises through efflux pumps and ribosomal protection proteins (34). Increasing resistance necessitates careful selection of antibiotics and consideration of combination therapies to overcome these mechanisms.

M. pneumoniae is a unique, small bacterium lacking a cell wall, a trait which makes it inherently resistant to beta-lactam antibiotics (35). It is a common cause of atypical pneumonia, especially in children and young adults, and is also associated with other respiratory infections. This bacterium exhibits resistance primarily to macrolides, the preferred

treatment option, through mutations in the 23S rRNA of the 50S ribosomal subunit, which reduce drug binding (36). This resistance can lead to treatment failures and the need for alternative antibiotics such as tetracyclines or fluoroquinolones. The absence of a cell wall and the bacterium's intrinsic resistance to certain antibiotics pose challenges for treatment and highlight the need for new therapeutic approaches and monitoring resistance patterns.

Recent advances to combat pathogen resistance

Recent advances in genomics have revolutionized our understanding of antimicrobial resistance. High-throughput sequencing technologies allow for rapid and detailed analysis of microbial genomes, revealing resistance genes and their mechanisms. CRISPR technology is being explored not only for gene editing but also as a tool to combat antibiotic resistance (37,38). By targeting and inactivating resistance genes, CRISPR-based strategies offer a promising approach to restore the efficacy of existing antibiotics.

Antibiotic stewardship programs aim to optimize the use of antibiotics to combat resistance. These programs involve coordinated efforts to prescribe antibiotics at the right dose and duration (39). New aspects of these programs include integrating advanced diagnostic tools and real-time data analytics to guide clinical decisions. For example, rapid diagnostic tests can quickly identify pathogens and their resistance profiles, allowing for more targeted therapy and reducing the misuse of broad-spectrum antibiotics.

Bacteriophage therapy, which uses viruses that specifically infect bacteria, is being revisited as a potential alternative to antibiotics. Phages can be engineered to target multi-drug-resistant bacteria, and their specificity reduces the risk of disrupting the normal microbiota (40). Advances in synthetic biology have enhanced the ability to design phages with improved efficacy and safety profiles. Clinical trials and case studies have demonstrated phage therapy's potential in treating infections resistant to conventional antibiotics (41).

The discovery and development of AMPs and other novel compounds offers new avenues for tackling resistant pathogens. AMPs are part of the innate immune system and exhibit broad-spectrum activity against bacteria, viruses, and fungi (42). Research into synthetic and natural AMPs is progressing, with several candidates showing promise in preclinical and clinical studies (43). Additionally, the exploration of novel chemical scaffolds and drug repurposing efforts are uncovering new antimicrobial agents that could circumvent existing resistance mechanisms (44).

The human microbiome plays a critical role in health and disease, including the development and spread of antibiotic resistance. New research is focusing on microbiome modulation as a strategy to combat resistance (45). Probiotics, prebiotics, and fecal microbiota transplantation (FMT) are being investigated for their potential to restore healthy microbial communities and outcompete resistant pathogens. Understanding the interactions between the microbiome and pathogenic bacteria can lead to innovative treatments that support the natural defenses of the human body.

Global surveillance systems and the use of big data are crucial for tracking the emergence and spread of resistance. Enhanced surveillance involves not only the monitoring of resistance patterns but also the collection of data on antibiotic use and outcomes (46). Integrating big data analytics and machine learning algorithms allows for the identification of trends, the prediction of resistance hotspots, and the development of targeted interventions (47). International collaborations and data-sharing initiatives are essential for a coordinated global response to antibiotic resistance.

CONCLUSIONS

In conclusion, antimicrobial resistance, exemplified by organisms such as *S. pneumoniae*, *H. influenzae*, and *M. pneumoniae*, underscores the complex challenges in treating bacterial infections. Each pathogen has developed specific mechanisms to evade antimicrobial action, necessitating vigilant monitoring, judicious use of antibiotics, and continuous research into novel therapeutic strategies. Addressing pathogen resistance is crucial for ensuring effective treatment and controlling the spread of resistant infections.

The landscape of antimicrobial resistance is continuously evolving, presenting new challenges and opportunities. Advances in genomics, innovative therapeutic approaches, and enhanced surveillance efforts are at the forefront of combating resistance. By leveraging these new aspects, the scientific and medical communities can develop more effective strategies to preserve the efficacy of existing antibiotics and discover new treatments, ultimately improving patient outcomes and public health. Addressing antimicrobial resistance requires a multifaceted approach, integrating cutting-edge research, clinical practice, and global cooperation.

Conflict of interest
The authors declare that they have no conflict of interest.

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