



BACTERIAL AIRWAY INFECTIONS AND ANTIBIOTIC RESISTANCE TO THE MOST COMMON BACTERIA

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ABSTRACT

Frequent use of antibiotics against bacterial infections can lead to the development of resistant bacterial strains, posing a public health problem. The biochemical mechanisms by which bacteria develop resistance are varied and complex, and sometimes unclear. Bacteria can create resistance through various mechanisms including hydrolyzing the beta-lactam ring of penicillins and cephalosporins, modifying aminoglycosides, or by mutation of the antibiotic target site. Bacteria also create resistance through membrane protein efflux pumps that expel antibiotics from bacterial cells, or by altering the permeability of the cell wall. The most common bacteria in the respiratory tract are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Staphylococcus aureus*. Pneumococci are susceptible to penicillins (beta-lactams), but over the years they have developed resistance, preventing the antibiotic from inhibiting the synthesis of bacterial peptidoglycan. Macrolides used to treat pneumococcal infections have led to the emergence of macrolide-resistant species of *S. pneumoniae*. Resistance can be of varying degrees, ranging from intermediate to high. Strains of *S. pneumoniae* can be resistant to erythromycin and azithromycin. In cases of macrolide resistance, cephalosporin is used as a second choice, although resistance to newer antibiotics is low. The most common antibiotic treatment for beta-lactamase-producing *H. influenzae* infections is the combination of amoxicillin and clavulanic acid, and *Haemophilus* resistance to penicillin and ampicillin ranges from 25 to 60%. In adults, the antibiotic of choice in pneumonia caused by *M. pneumoniae* are macrolides, tetracyclines, and fluoroquinolones. Only sporadic cases of *M. pneumoniae* resistance to macrolides have been noted; while there are insufficient epidemiological data on *C. pneumoniae* resistance to macrolides. *S. aureus* is resistant to methicillin, but has also become resistant to other antibiotics such as oxacillin, penicillin, and amoxicillin. Bacterial infections of the airways can cause various diseases such as bronchitis and pneumonia. Understanding the pathogenic mechanisms of infection and resistance patterns is important for effective treatment and the prevention of antibiotic resistance.

KEYWORDS: Bacteria, resistance, antibiotic resistance, infection, respiratory

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INTRODUCTION

The inappropriate use of antibiotics in the treatment of diseases caused by bacterial infections, in which they are not required, determines the development of resistant bacterial strains, in addition to needlessly exposing the patient to adverse reactions of pharmacological treatment and inducing a waste of economic resources (1). Resistant bacteria can be found in many organs and tissues and understanding the mechanisms of resistance that cause airway infections is crucial for treatment and is a significant public health challenge (2).

The mechanisms by which bacteria develop resistance are varied and complex and often involve genetic and biochemical changes (3) (Table I). Bacteria can produce enzymes that degrade or modify antibiotics, rendering them ineffective (4). Some enzymes hydrolyse the beta-lactam ring of penicillins and cephalosporins, while others modify aminoglycosides that acetylate, phosphorylate, or adenylate aminoglycosides, preventing their binding to bacterial ribosomes (5).

Table I. Some of the mechanisms utilized by bacteria to develop resistance.

<i>Intrinsic resistance:</i>	The natural and intrinsic ability of bacteria to resist antibiotics.
<i>Cell wall impermeability:</i>	Impermeability to several antibiotics (e.g., Gram-negative bacteria).
<i>Efflux pumps:</i>	Transport proteins involved in the expulsion of toxic substances, including antibiotics.
<i>Acquired resistance:</i>	Occurs when bacteria develop resistance through mutation or by acquiring resistance genes.
<i>Genetic mutations:</i>	Mutations can alter the target site of the antibiotic within the bacterium.
<i>Target modification:</i>	Bacterial mutations alter their cellular targets, reducing the binding affinity of antibiotics.
<i>Enzymatic modification or degradation:</i>	Bacteria can produce enzymes that chemically modify or degrade the antibiotic.
<i>Gene transfer and transformation:</i>	Bacteria can take up free DNA from the environment, which may contain resistance genes.
<i>Transduction:</i>	Bacteriophages can transfer resistance genes from one bacterium to another.
<i>Conjugation:</i>	Bacteria can transfer genetic material directly to another bacterium.
<i>Beta-lactam resistance:</i>	Enzymes that hydrolyze the beta-lactam ring, such as penicillinase.
<i>Glycopeptide resistance:</i>	Plasmids can carry multiple resistance genes.

In another type of inactivation, bacteria can mutate or change the target site of the antibiotic, reducing the binding affinity of the drug, as occurs in methicillin-resistant *Staphylococcus aureus* (6). In this case, beta-lactam antibiotics can no longer bind effectively. In addition, ribosomal mutations can lead to resistance to antibiotics such as tetracyclines and macrolides by altering the ribosomal binding site (7).

Some bacteria cause resistance by altering the permeability of the cell wall or membrane to reduce the absorption of antibiotics (9). Efflux pumps, membrane proteins that actively expel antibiotics from bacterial cells, can cause a decrease in the intracellular concentration of the drug (8). Changes in porin channels can decrease the entry of beta-lactams and other antibiotics (10). Bacterial resistance can also occur through alternative metabolic pathways that bypass the target of the antibiotic.

DISCUSSION

The most common etiologic agents in respiratory and bacterial infections are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumonia*, *Chlamydia pneumoniae*, and *Staphylococcus aureus*.

Streptococcus pneumoniae

Pneumococci are germs that are highly sensitive to penicillins, both natural ones, such as penicillin G, and semi-synthetic ones, such as aminopenicillins (amoxicillin). The chemosensitivity of pneumococci to beta-lactams has undergone a significant change over the years due to the development of new local resistance.

Penicillin was produced in 1940 and was the first antibiotic used in infectious diseases, but already in 1970, penicillin-resistant strains of *S. pneumoniae* appeared with structural modifications of the penicillin-binding proteins of the bacterium that prevented the antibiotic from inhibiting the synthesis of bacterial peptidoglycan (11). Macrolides were therefore used to treat pneumococcal infections (12). However, the frequent use of these drugs led to the appearance of species of *S. pneumoniae* that were also resistant to macrolides. The most common mechanisms of macrolide resistance are ribosomal methylation mediated by the *erm*(B) gene and the synthesis of efflux pumps mediated by the *mef*(A) gene (13).

Penicillin-resistant strains of *S. pneumoniae* can be divided into intermediate-resistant or highly resistant strains. The minimum inhibitory concentration (MIC) is defined by the threshold concentration ($\mu\text{g}/\text{ml}$) to express the sensitivity and resistance of microorganisms to penicillin. Values between 0.12 and 1 $\mu\text{g}/\text{ml}$ indicate intermediate resistance and values greater than 2 $\mu\text{g}/\text{ml}$ indicate high resistance (14).

The distribution of MIC varies considerably in different geographical areas. The percentage of *S. pneumoniae* strains with intermediate resistance to penicillins is approximately 15% in North America, 27% in South America, and 11.2% in Europe. In cases of respiratory infections caused by penicillin-resistant strains of *S. pneumoniae*, high-dose amoxicillin-clavulonate (80-90 mg/kg/day) is administered, thus achieving antibiotic sensitivity rates of 99% (15). The MIC breakpoints used to distinguish macrolide-resistant strains of *S. pneumoniae* are 1 microgram per ml for azithromycin and 0.5 $\mu\text{g}/\text{ml}$ for erythromycin. Erythromycin-resistant strains in Europe are approximately 10% (16). In cases of macrolide resistance, a third-generation cephalosporin is used and, as a second choice, one of the antibiotics such as fluoroquinolones (levofloxacin, moxifloxacin, and others), ketolides (telithromycin), and oxazolidones (linezolid) (17,18). Resistance to these newer antibiotics is rare (about 0.12%).

Streptococcus pyogenes

The mechanism of resistance of *S. pyogenes* to penicillins is linked to the selection of strains producing beta-lactamases (19). Although increasing, the resistance of these strains to penicillins is still a limited phenomenon. *S. pyogenes* resistance to macrolides is instead worrying. One study showed that its incidence in some European countries is about 38% (20). Of the erythromycin-resistant strains of *S. pyogenes*, 63% have an M phenotype, 26% an R phenotype (inducible resistance), and 11% an RC phenotype (constitutive resistance). Strains with the first phenotype possess efflux pumps that confer a low degree of resistance to erythromycin while maintaining sensitivity to clindamycin and 16-carbon (C) macrolides (21). Those with the second phenotype have a low level of resistance to erythromycin and resistance to clindamycin and 16-C macrolides that are inducible by exposure to subinhibitory concentrations of erythromycin (22). Finally, strains with the third phenotype have a high level of resistance to both macrolides and clindamycin (23). The resistance mechanism in strains with the RI and RC phenotypes is represented by the methylation of the bacterial rRNA, the target site of the drug (24). The erythromycin resistance of *S. pneumoniae* has made macrolides second-choice drugs in the treatment of respiratory infections with this etiology, for example, in acute pharyngotonsillitis.

Haemophilus influenzae

The antibiotic treatment of choice for *H. influenzae* infections is the combination of amoxicillin and clavulanic acid (25). Recently, beta-lactamase-producing strains of *Haemophilus* have become widespread. It is estimated that *Haemophilus* resistance to penicillin and ampicillin varies from 25 to 60% (26). This incidence has increased in recent years following the use of the heptavalent vaccine which has led to a reduction in infections caused by *S. pneumoniae*, at the expense of an increase in those caused by *H. influenzae*.

Moraxella catarrhalis

M. catarrhalis and *H. influenzae* produce beta-lactamases, enzymes that attack and destroy the beta-lactam ring, a key component of beta-lactam antibiotics such as penicillins and cephalosporins (27). Since the beta-lactam ring is essential for the effectiveness of these antibiotics, its destruction prevents the antibiotics from working, consequently the bacteria that produce beta-lactamases become resistant and continue to proliferate even in the presence of antibiotics. For this reason, the administration of the combination of amoxicillin and clavulanic acid should be preferred to the administration of amoxicillin alone (28).

Mycoplasma pneumoniae

The antibiotics of choice in pneumonia caused by *M. pneumoniae* are macrolides, tetracyclines, and fluoroquinolones, however, they are not recommended in pediatric age (29). In the last three decades, only sporadic cases of *M. pneumoniae* resistance to macrolides have been reported, except in Japan (30). In the world, 3 cases of erythromycin-resistant cases were reported in Israel in the 1980s, 2 cases in the United States and Finland between 1995 and 1999, and 2 cases in France in 1999. Japan differs from other geographical areas in that since the year 2000, numerous strains of macrolide-resistant *M. pneumoniae* have been isolated and in 2004, the macrolide-resistance of *M. pneumoniae* was estimated at 15%.

The development of resistance seems to be due to a new sequence of the PI adhesin gene, the most important adhesion molecule of *M. pneumoniae*, that favors the pathogenic action of the bacterium and stimulates the inflammatory response in the host (31). The new sequence is characterized by a point mutation in the V domain of the 23s rRNA that involves the replacement of alanine with guanine in positions 2,058 and 2,059. Although macrolide-resistant mycoplasma strains have not yet found widespread diffusion in the world, the experience of Japan requires careful epidemiological surveillance.

Chlamydia pneumoniae

Regarding the resistance of *C. pneumoniae* to macrolides, no epidemiological data are available to date (32). Resistance of chlamydia to antibiotics is generally rare, and while some cases of *in vivo* resistance of *Chlamydia trachomatis* and *Chlamydia suis* species to macrolides have been reported in the literature, only *in vitro* studies have been carried out on the resistance of *C. pneumoniae* (33). From these, it has resulted that *C. pneumoniae* does not develop resistance to high doses of antibiotics and responds even to low doses of macrolides. (34). However, genetic modifications have been found in some strains that could determine the development of macrolide resistance in *C. pneumoniae* over time (35). For this reason, prolonged treatment with macrolides, which is a trigger for the development of antibiotic resistance, should be avoided whenever possible.

Staphylococcus aureus

S. aureus is a methicillin-resistant bacterium, but it has also become resistant to other antibiotics such as oxacillin, penicillin, and amoxicillin (36). Resistance to this bacterium can cause a variety of infections including less serious skin infections, pneumonia, blood infections, and post-surgical infections. Resistance to this bacterium is due to the presence of a *mec(A)* gene, which encodes a penicillin-binding protein that has a low affinity for beta-lactam antibiotics (37). This protein protects the bacterium's cell wall, allowing it to carry out its pathogenic action even in the presence of the antibiotic. Resistance to infection occurs primarily in hospitals and nursing homes, but it can also occur in healthy individuals who have not been hospitalized (38). *S. aureus* resistance can be transmitted mainly through direct contact with an infected wound or objects that have touched infected tissue (39). Bacterial resistance is difficult to treat due to the resistance of many common antibiotics that are available on the market. However, some antibiotics such as vancomycin, linezolid, and daptomycin can be effective (40). If resistance persists, surgical intervention may be performed to remove infected tissue (41).

CONCLUSIONS

The most common bacteria that cause airway infections include *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, *M. catarrhalis*, *M. pneumoniae*, *C. pneumoniae*, and methicillin-resistant *S. aureus*. Bacterial airway infections can range from mild to severe and can cause diseases such as sinusitis, bronchitis, and pneumonia. Clarifying the mechanisms of infection and resistance patterns in the infections is essential for effective treatment and prevention of antibiotic resistance. Accurate diagnosis, appropriate use of antibiotics, and preventive measures are important in managing bacterial airway infections.

Conflict of interest

The authors declare that they have no conflict of interest.

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