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TWO CLASSES OF ANTIBIOTICS, BETA-LACTAMS AND MACROLIDES, WHICH ARE COMMONLY USED FOR THE TREATMENT OF INFECTIONS

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ABSTRACT

Infections, particularly respiratory ones, are often treated with two classes of antibiotics, beta-lactams and macrolides, which inhibit bacterial growth. Beta-lactams exert their effect by inhibiting the synthesis of the bacterial cell wall, while macrolides (bacteriostatic antibiotics) work by inhibiting the bacterial protein synthesis. The beta-lactams imitate the natural substrate of penicillin-binding proteins (PBPs) and bind to specific proteins, while the macrolides achieve this by binding to the 50S ribosomal subunit of the bacterial ribosome. Common types of beta-lactams include penicillins, cephalosporins, carbapenems, and monobactams. For macrolides, common types include erythromycin, clarithromycin, and azithromycin. The choice of antibiotic for treatment is based on the type of infection, the characteristics of the microbe, and the physiopatological aspect of the patient. Beta-lactams and macrolides antibiotics act through complex mechanisms that are not yet completely clear and therefore, further insights on this theme would help to formulate a better and more precise therapy.

KEYWORDS: *antibiotic, beta-lactam, macrolide, quinolone, infection*

INTRODUCTION

The pharmacological criteria underlying the effect of antimicrobials has been better understood in the last 10 years. Beta-lactams and macrolides are two classes of antibiotics commonly used in the treatment of respiratory infections. They work through different mechanisms to inhibit bacterial growth and are often chosen based on the type of infection and the suspected or known causative organism. The clinical efficacy of an antibiotic is related to the mechanism of action and chemosensitivity (pharmacodynamics), to the patient's exposure to the drug (pharmacokinetics), and the pharmacokinetic/pharmacodynamic relationship (1).

Beta-lactams are a broad class of antibiotics that include penicillins, cephalosporins, carbapenems, and monobactams (2). They share a common structural feature: a beta-lactam ring, which is essential for their antibacterial activity. Beta-lactams exert their effect by inhibiting bacterial cell wall synthesis (3). The bacterial cell wall is composed of peptidoglycan, a polymer that provides structural integrity. The synthesis of peptidoglycan involves a series of enzymatic steps, one of which is the cross-linking of the peptidoglycan strands by penicillin-binding proteins (PBPs) (4). Beta-lactams mimic the natural substrate of PBPs and bind to these proteins, thereby inhibiting their activity (2). This inhibition

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prevents the cross-linking of peptidoglycan strands, leading to a weakened cell wall and ultimately causing bacterial cell lysis due to osmotic pressure (5).

Macrolides are another class of antibiotics that include drugs such as erythromycin, azithromycin, and clarithromycin. These antibiotics are characterized by a large macrocyclic lactone ring. They work by inhibiting bacterial protein synthesis by binding to the 50S ribosomal subunit of the bacterial ribosome (6,7). This binding interferes with the translocation steps in protein synthesis, specifically by blocking the exit tunnel from which newly synthesized polypeptides emerge (8). As a result, the elongation of the protein chain is interrupted, leading to the cessation of bacterial growth (9). This mechanism classifies macrolides as bacteriostatic antibiotics, meaning they inhibit the growth and reproduction of bacteria rather than directly killing them.

DISCUSSION

The two classes of antibiotics commonly used in the treatment of respiratory infections are beta-lactams and macrolides. Beta-lactams work by inhibiting the synthesis of the bacterial cell wall. They bind to PBPs located inside the bacterial cell wall, preventing the cross-linking of peptidoglycan chains, which are essential for cell wall strength and rigidity. This leads to cell lysis and death, particularly in actively growing bacteria.

Beta-lactams vary in their spectrum of activity (Table I). Penicillins are generally effective against Gram-positive bacteria, while cephalosporins and carbapenems have broader spectrums that include both Gram-positive and Gram-negative bacteria.

Table I. *Common types of beta-lactams and their uses in treating respiratory infections.*

Beta-lactams common types	
Penicillins:	*Penicillin, Amoxicillin, Ampicillin*
Cephalosporins:	*Ceftriaxone, Cefuroxime, Cephalexin*
Carbapenems:	*Imipenem, Meropenem*
Monobactams:	*Aztreonam*
Common uses in respiratory infections	
Community-Acquired Pneumonia (CAP):	*Amoxicillin, Ceftriaxone*
Acute Otitis Media:	*Amoxicillin*
Sinusitis:	*Amoxicillin-Clavulanate*
Streptococcal Pharyngitis:	*Penicillin*

Resistance to beta-lactams can occur through the production of beta-lactamases, enzymes that break down the beta-lactam ring, rendering the antibiotic ineffective (10). This has led to the development of beta-lactamase inhibitors (e.g., clavulanate) that are combined with beta-lactams to overcome resistance (11).

Beta-lactams, which include penicillins and cephalosporins, have a similar mechanism of bactericidal action, characterized by the inhibition of the synthesis of peptidoglycan in the bacterial wall. All beta-lactams are made up of an azetidine tetratomic ring (6-aminopenicillanic acid in penicillin, and 7-aminocephalosporadic acid in cephalosporins) which represents a structural analogue of the dextro-alanine dimer, the substrate of bacterial transpeptidases (protein binding proteins penicillins) (12). The binding of the beta-lactam to the transpeptidase enzyme leads to the denaturation of the enzyme and an arrest of the synthesis of the peptidoglycan, and consequently of bacterial growth (13). This mechanism represents the bacteriostatic effect of the antibiotic.

The bactericidal effect is secondary to the genomic depression of murein hydrolases which demolish the murein of the cell wall of the prokaryotic cell and cause its lysis (14). Sensitive beta-lactamase antibiotics, such as amoxicillin, are generally administered in combination with beta-lactamase inhibitors, such as clavulanic acid which, despite having the beta-lactam ring, lacks intrinsic antibacterial activity (2). Beta-lactamase inhibitors bind to beta-lactamases, enzymes responsible for beta-lactam hydrolysis, and inactivate them with a suicidal mechanism. Thanks to this mechanism, clavulanic acid preserves the activity of amoxicillin against *Streptococcus pneumoniae*, methicillin-sensitive *Staphylococcus aureus* species, *Haemophilus influenza*, and *Moraxella catarralis* (15-17). Among beta-lactams, third-

generation cephalosporins (e.g. ceftriaxone, cefixime, cefpodoxime) commonly used in respiratory infections have a broader antibacterial spectrum than penicillins, including enterobacteria such as *Klebsiella*, *Serratia*, *Enterobacter*, and *Clostridia*, due to a greater sensitivity towards plasmid beta-lactamases and good intrinsic activity (18). This class of cephalosporins also includes some antibiotics, such as ceftazidime and cefoperazone, which are also active on *Pseudomonas aeruginosa* (18).

Macrolides inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit. This action blocks the translocation step in protein synthesis, preventing the growth of the bacterial cell (6). Macrolides are primarily effective against Gram-positive bacteria and some Gram-negative bacteria, as well as atypical pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* (19) (Table II).

Table II. *Common types of macrolides and uses in treating respiratory infections.*

Common types of macrolides	
Erythromycin	
Clarithromycin	
Azithromycin	
Common uses in respiratory infections	
Community-Acquired Pneumonia (CAP):	*Azithromycin, Clarithromycin*
Acute Bronchitis:	*Azithromycin*
Pertussis (Whooping Cough):	*Erythromycin, Azithromycin*
Pharyngitis and Tonsillitis (in penicillin-allergic patients):	*Azithromycin, Clarithromycin*

Resistance to macrolides is often due to modification of the target site in the ribosome, efflux pumps that expel the drug from the bacterial cell, or enzymatic degradation (20). This can limit their effectiveness, particularly in certain regions or settings with high levels of resistance.

The macrolides Azithromycin, Clarithromycin, Erythromycin, and Fidaxomicin are antibiotics with bacteriostatic activity that can sometimes carry out a bactericidal action. This occurs in cases of infection with germs that are very sensitive to macrolides, such as *streptococci* and *pneumococci*. Their mechanism of action consists in the inhibition of bacterial protein synthesis through attachment to the 50s ribosomal subunit containing peptidyl transferase, an enzyme that catalyzes the formation of the bond between amino acids and the polypeptide chain in formation (21). Macrolides therefore act only on inactive cell proliferation.

Their spectrum of action is medium and includes, in addition to intracellular pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, also Gram-positive cocci such as *staphylococci*, *streptococci*, *pneumococci* and Gram-positive bacilli such as *Nocardia* and *Listeria*, and some Gram-negative bacteria such as *Bordetella pertussis* and *Bordetella catarralis*. New-generation antibiotics include fluoroquinolones, ketolins, and oxazolidinones. While beta-lactams and macrolides are used in all respiratory infections, quinolones are used only in CAPs resistant to other antibiotics (22).

Among the quinolones, we distinguish the derivatives of nalidixic acid or first-generation quinolones, and the fluoroquinolones which include second and third-generation quinolones. First-generation quinolones such as oxalinic acid, pipemic acid, and others, have a narrow antibacterial spectrum mainly oriented towards enterobacteria, and a pharmacokinetics which, due to rapid elimination and specific tissue rates, allows their use only as urinary antiseptics.

Second-generation fluoroquinolones are characterized by the addition of a fluorine atom to carbon 6, which gives the molecule a highly reinforced and extended activity on Gram-negatives and a reduced urinary elimination (23). Third-generation fluoroquinolones were obtained by adding a heterocyclic substituent at position 7, which broadens their spectrum of action to Gram-positives (24). Third-generation fluoroquinolones such as levofluoxacin and maxifluoxacin are a valid alternative in CAP therapy caused by resistant strains, as they are active against typical agents such as pneumococcus, and atypical agents such as chlamydia and mycoplasmas, as well as on anaerobes and mycobacteria.

These are bacterial antibiotics that bind irreversibly to the A subunit of DNA gyrase (mouse second isomerase), the enzyme responsible for the supercoiling of bacterial DNA, hindering the replication and survival of the bacterium (25). Third-generation fluoroquinolones differ from first- and second-generation quinolones in that they also exert an inhibitory

action on topoisomerase IV, an enzyme homologous to DNA-gyrase with high decatenating power (23). This action would broaden the spectrum of action of quinolones to Gram-positive bacteria. In the 1990s, linezolid was synthesized, a morpholino derivative belonging to the oxazolidinone class, indicated in systemic infections caused by strains resistant to other antibiotics (26). The drug exerts a bacteriostatic action by binding to the 50s ribosomal subunit and is available both in preparation for oral use and for systemic use (27). In pediatrics, it has been used without side effects, as well as for a long time in patients with cystic fibrosis.

Finally, telithromycin belongs to a new class of antibiotics, the ketolides. It is chemically derived from macrolides and therefore equipped with the same mechanism of action but is more effective against Gram-positive cocci (28). The new chemical structure gives the molecule a greater binding affinity to the ribosomes of MLSb pneumococcal strains resistant to lycosamide macrolides and *Streptogramin B* (29). Both linezolid and telithromycin are reserved for the treatment of complicated CAPs.

In some cases, combination therapy is utilized with beta-lactams and macrolides to provide broad coverage, especially for severe or hospitalized cases of pneumonia, where atypical pathogens might be involved (30,31). Beta-lactams can cause allergic reactions in some individuals, ranging from mild rashes to severe anaphylaxis. Macrolides are generally well-tolerated but can cause gastrointestinal disturbances and, less commonly, QT prolongation.

CONCLUSIONS

Beta-lactams and macrolides are cornerstone antibiotics in the treatment of respiratory infections. Their selection is based on the type of infection, the suspected pathogens, and patient-specific factors such as allergies and resistance patterns. Both beta-lactams and macrolides are crucial in the fight against bacterial infections, but they target different aspects of bacterial physiology. Beta-lactams disrupt cell wall synthesis, causing bacterial cell death, while macrolides inhibit protein synthesis, preventing bacterial growth and proliferation. Knowledge of these mechanisms is essential for the effective use of these antibiotics in clinical practice and for developing new strategies to combat antibiotic resistance.

Conflict of interest

The authors declare that they have no conflict of interest.

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