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Piperacillin/Tazobactam: an update for clinical use

Alice R. C. e C. Costa,[1] Andréia Patrícia Gomes,[2] Eduardo Vinícius V. Varejão,[3] Rodrigo Siqueira-Batista[4,5*]

Abstract

Introduction: Piperacillin-tazobactam, a broad-spectrum penicillin, represents a crucial option in the treatment of infections, especially in critically ill patients who exhibit high rates of resistance to various antimicrobial agents. It is of paramount importance to understand this medication and its updates regarding its clinical use to inform precise therapeutic choices aimed at optimizing patient care. Objective: To describe the main pharmacological and therapeutic aspects of piperacillin-tazobactam, highlighting its clinical application and updates related to its use. Methods: A narrative review of the literature was conducted to provide an update on the most relevant aspects related to piperacillin-tazobactam, including (1) a brief history; (2) chemical structure; (3) mechanism of action; (4) resistance mechanisms; (5) spectrum; (6) major clinical uses; and (7) adverse effects. Results: The safe use of piperacillin-tazobactam necessitates rapid testing for antimicrobial resistance patterns, discouraging its empirical use in cases of ESBL-producing microorganisms. In patients undergoing renal replacement therapy, it is crucial to establish antibiotic goals promptly. For critically ill patients, monitoring pharmacodynamic and pharmacokinetic variability is essential. Conclusion: Piperacillin-tazobactam remains a vital drug in the management of critically ill patients, requiring constant updates. Furthermore, there is a need for further studies, especially concerning its continuous use and the selection of alternatives to carbapenem-resistant medications.

Keywords: Anti-Bacterial Agents; Piperacillin, Tazobactam Drug Combination; beta-Lactams.

1. Medical student, School of Medicine, Federal University of Viçosa, Viçosa, MG, Brazil.
2. Associate Professor in the Department of Medicine and Nursing, Federal University of Viçosa, Viçosa, MG, Brazil.
3. Associate Professor in the Department of Chemistry, Federal University of Viçosa, Viçosa, MG, Brazil.
4. Full Professor at the School of Medicine, Faculdade Dinâmica do Vale do Piranga (FADIP), Ponte Nova, MG, Brazil.
5. Associate Professor in the Department of Medicine and Nursing, Federal University of Viçosa, Viçosa, Minas Gerais, Brazil.

*Correspondence address:
E-mail: lmecs@ufv.br
ORCID: https://orcid.org/0000-0002-3661-1570

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Introduction

Penicillins are part of a group of antibiotics called beta-lactams, chemically characterized by having a beta-lactam ring fused to a thiazolidine ring. This bicyclic structure corresponds to 6-aminopenicillanic acid (6-APA), the structural backbone of all penicillins. Various penicillins, both natural ones obtained by fermentation of *Penicillium chrysogenum* (penicillins G and V) and semisynthetic ones, differ from each other by the type of side chain attached to the amino group of the 6-APA structural backbone (Figure 1). The penicillin group is usually divided into five classes: natural penicillins (G and V); penicillinase-resistant penicillins (methicil-

lin, nafcillin, and isoxazolyl); aminopenicillins (amoxicillin and ampicillin); carboxypenicillins (carbenicillin and ticarcillin); and ureidopenicillins (azlocillin, mezlocillin, and piperacillin).[1]

The discovery of this group occurred in 1928 when Alexander Fleming observed that the contamination of a culture of *Staphylococcus aureus* with the fungus *Penicillium notatum* (currently *Penicillium chrysogenum*) resulted in the lysis of bacterial cells. The substance responsible for the antibacterial activity of the fungus was named penicillin and would revolutionize the prognosis of bacterial diseases.[2] A significant breakthrough in the development of new antibiotics came with the isolation of the structural backbone of penicillins, 6-aminopenicillanic acid (6-APA), from which various other penicillins were developed through chemical alterations in the side chain attached to the amino group of this central structure. Even today, the penicillin group is responsible for changing the prognosis of many diseases, being the subject of numerous studies, for example, for use in critically ill patients as an alternative to carbapenems, which seem to be responsible for an increase in the selection of resistant bacteria.[3]

The primary mechanism of action of penicillins is the inhibition of bacterial cell wall synthesis. This group binds to peptidoglycan-binding proteins (PBPs), more commonly known as penicillin-binding proteins (PBPs), which are responsible for essential enzymatic activities in the biosynthesis of new peptidoglycan molecules, a crucial component of the forming bacterial cell wall. Binding to these proteins results in a defect in cell wall construction, leading to cell lysis.[1,2]

The expanded spectrum of piperacillin against Gram-negative bacteria, distinguishing it from other penicillins, is due to its high affinity for the PBPs of these microorganisms, including strains of *Pseudomonas aeruginosa*, *Enterobacteriaceae*, *Bacteroides* spp, and *Enterococcus faecalis*.[4,5] On the other hand, tazobactam is part of beta-lactamase inhibitors, being a sulfone of penicillanic acid that irreversibly binds to beta-lactamase enzymes, forming a stable acyl-enzyme complex, allowing piperacillin to be effective against bacteria producing beta-lactamases.[4,5] The combination of piperacillin and tazobactam provides piperacillin with the broadest spectrum among all penicillins.[5]

Currently, in Brazil, piperacillin-tazobactam is indicated for hospital infections caused by various microorganisms, generally encompassing critically ill patients.[2] Due to high resistance rates related to the drugs of choice in the treatment of these patients, especially among extended-spectrum beta-lactamase (ESBL) producing microorganisms, piperacillin-tazobactam has been considered as a possible alternative in treatment. Furthermore, it is known that these patients have pathophysiological changes that impact treatment success and require the best therapeutic choices, including specific doses due to the severity of the condition.[6,7] As a result, constant reviews are necessary to update therapeutic choices.

Recognizing the importance of updates on this subject, this article aims to revisit the knowledge about the antibiotic piperacillin-tazobactam, describing the main consolidated information, such as mechanism of action, resistance mechanisms, among others, combined with current information regarding clinical use to assist healthcare professionals in their decision-making.

Methods

In this scientific article, concerning the methodological nature, a narrative literature review was conducted, which is characterized as "*not using explicit and systematic criteria for literature search and critical analysis*" (p. 2) and does not employ "*sophisticated and exhaustive search strategies*" (p. 2).[8] This review aims to update the main pharmacological and therapeutic as-

pects related to piperacillin-tazobactam. Unlike a systematic review, therefore, which aims to answer a specific question related to a particular subject matter issue, the literature research used does not require a detailed description of the "*methodology for searching for references, nor [of] the criteria used in the evaluation and selection of the works consulted*" (p. 50)[9], with the purpose of outlining a "*state of the art of a particular subject, from a theoretical or contextual perspective*" (p. 1).[10]

In this context, we proceeded with the identification and meticulous analysis of bibliographic sources, including articles, books, and publications from reputable scientific institutions. This process was conducted based on the researchers' prior knowledge, adopting a rigorous approach in the comprehensive reading of these sources, followed by a critical evaluation aimed at extracting the most pertinent and relevant information. The sources consulted, written in both English and Portuguese, served as the foundation for organizing the following topics that constitute this study: (1) brief history; (2) chemical structure; (3) mechanism of action; (4) resistance mechanisms; (5) spectrum; (6) major clinical uses; and (7) adverse effects.

Brief history

Penicillin was discovered in 1928 by Alexander Fleming, through the observation of the *Penicillium notatum* fungus, now called *Penicillium chrysogenum*, which contaminated a culture of *Staphylococcus aureus* at St. Mary's Hospital in London.[1,2] Fleming realized that the fungus produced an antimicrobial substance, and this substance was named penicillin.[2] In 1940, Florey, Chain, and their associates isolated penicillin, enabling the commercialization of penicillin G, which revolutionized the prognosis of infectious diseases.[1,2] The emergence of organisms producing beta-lactamases drove the development of components resistant to the hydrolysis of these microorganisms and the search for agents more effective than penicillin G against Gram-negative organisms. With the advent of this research, in 1959, Batchelor and col. successfully simplified the isolation of 6-aminopenicillanic acid (6-APA), which forms the central core of penicillin G. This discovery marked the beginning of the field of semi-synthetic penicillins, with part of the production obtained through fermentation and part obtained artificially by introducing radicals onto the core structure. This made it possible to produce and test various semi-synthetic penicillins, such as methicillin against beta-lactamase-producing *Staphylococcus aureus*, ampicillin against selected Gram-negative bacilli, among others. Since then, ongoing discoveries have sought drugs with various pharmacological and antimicrobial properties.[1,2]

Piperacillin, a member of the ureidopenicillin group, resulted from research aimed at identifying beta-lactams that are highly effective against *Pseudomonas* spp., have a broad spectrum of action, and are less toxic than aminoglycoside antibiotics. This antibiotic was introduced in 1976, as a derivative of ampicillin with the addition of a hydrophilic heterocyclic group to the gamma-amino group.[2,4] This substitution gave piperacillin a broad spectrum of action against Gram-negative bacteria, in part due to its increased affinity for penicillin-binding protein (PBP)-3.[5] However, piperacillin is inactivated by plasmid-derived beta-lactamases produced by some microorganisms, and it is often combined with tazobactam, a derivative of sulfone of penicillanic acid, to enhance its effectiveness against these microorganisms.[2,4]

Chemical structure

Piperacillin is a synthetic penicillin derived from ampicillin, with the chemical name (2S,5R,6R)-3,3-dimethyl-7-oxo-6-[(2R)-2-[(4-ethyl-2,3-dioxo-1-piperazinyl)formamido]-2-phenylacetami-

do]-4-thia-1-azabicyclo[3.2.0]-heptan-2-carboxylic acid (Figure 1).[11] It features the beta-lactam ring in its structure, common to all antimicrobials referred to as beta-lactams, including penicillins. A lactam corresponds to a cyclic amide.[12,13] Amides are characterized by the presence of a nitrogen atom directly bonded to a carbonyl group. Therefore, in lactams, the nitrogen and the carbonyl carbon are part of a cyclic structure. The Greek prefix "beta" indicates that the cycle consists of a total of four atoms.[14] In penicillins, the beta-lactam ring is fused to a five-membered thiazolidine ring. This bicyclic structure forms the structural backbone of all penicillins, and this structure is known as 6-aminopenicillanic acid (6-APA), biosynthetically formed by the cyclization of a dipeptide formed by the condensation between L-cysteine and D-valine. Ampicillin, as a side chain, has the (R)-2-amino-2-phenylacetyl group attached to the nitrogen at position 6 (N-6) of the central 6-APA skeleton. This structure is chemically formed by the linkage of this nitrogen to the carboxylic acid group of D-phenylglycine. Piperacillin, on the other hand, is synthesized from ampicillin by linking the amino group of the D-phenylglycine portion to a 4-ethylpiperazin-2,3-dione carbonyl group. In this way, piperacillin contains a piperazine ring in its structure, from which it derives its name (Figure 1).[11]

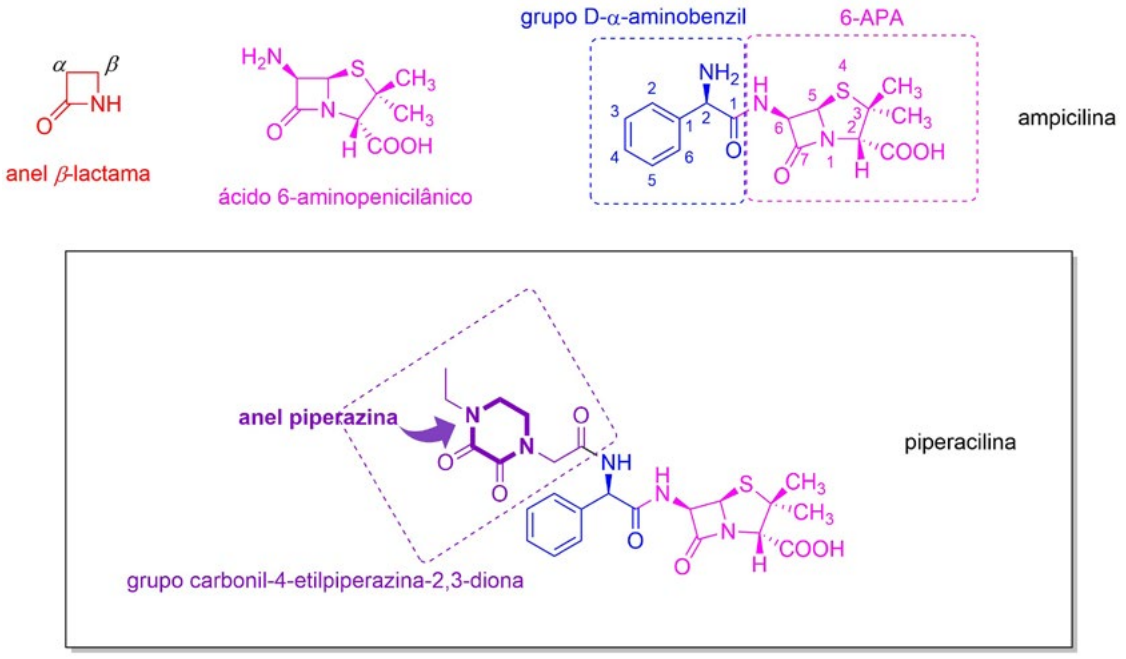

Figure 1. Chemical structures of the beta-lactam ring, 6-aminopenicillanic acid, ampicillin, and piperacillin. Note the piperazine ring as a constituent of the side chain in piperacillin.

Source: Self-generated image based on references.[12,15]

Mechanism of action

The mechanism of action is related to the presence of the beta-lactam ring. The drug binds to penicillin-binding proteins (PBPs), located on the external surface of the cytoplasmic membrane, preventing the formation of peptidoglycans, which are essential components of the bacterial cell wall, leading to osmotic lysis of bacterial cells.[2]

Piperacillin belongs to the group of penicillins, which act by inhibiting the synthesis of the bacterial cell wall. Bacteria require several enzymes to biosynthesize and link the constitu-

ents of their cell wall and PBP is responsible for the enzymatic activity of transglycosidases, transpeptidases, carboxypeptidases, and endopeptidases. Bacteria produce four types of PBPs, including high-molecular-weight PBP, low-molecular-weight PBP, which catalyze transpeptidation and carboxypeptidation, respectively, in cell wall assembly, and high-molecular-weight PBP class A, which are bifunctional enzymes with transpeptidase and transglycosylase domains. Penicillins bind to these proteins, inhibiting enzymatic actions and, consequently, the biosynthesis of new peptidoglycan molecules — the essential component of the bacterial cell wall —and their incorporation into the developing bacterial cell wall. Consequently, the cell in development has a defect in the formation of its cell wall, leading to osmotic lysis. Furthermore, the antibiotic action of penicillins also depends on the autolytic action of the bacteria's own enzymes on their cell wall, breaking down the old cell wall and providing the bactericidal effect of the drug, as the new cell wall will be defective. However, cells that are not actively multiplying or are osmotically protected can survive the presence of penicillin. This suggests that the bactericidal effect of penicillins is directly related to the cell cycle, where the binding of penicillin to PBPs disrupts an essential event, possibly occurring during cell division.[1]

Mechanism of resistance

There are four main mechanisms of resistance, which include the destruction of antibiotics by beta-lactamases, the inability to effectively penetrate Gram-negative bacteria, the efflux through the membrane, and low affinity of antibiotics to bind to PBPs.[1,16]

The primary mechanism of resistance to piperacillin is enzymatic inactivation of the drug caused by the production of beta-lactamases by microorganisms. Beta-lactamases are enzymes that catalyze the hydrolysis of the beta-lactam ring and are divided into four classes (A to D), based on the similarity of amino acid sequences and molecular structure. Classes A and C are the most clinically significant, class A enzymes are generally effectively inhibited by beta-lactamase inhibitors, unlike class C. However, point mutations can give rise to class A enzymes with an extended spectrum to penicilins, third-generation cephalosporins and aztreonam, referred to as extended-spectrum beta-lactamases (ESBL). Currently, the number of microorganisms producing ESBLs has increased, and it is controversial whether piperacillin-tazobactam is effective against these bacteria.[4] Class B enzymes are produced by some non-lactose-fermenting Gram-negative microorganisms, with plasmid-mediated enzymes having the broadest spectrum and resistance to all beta-lactam antibiotics except aztreonam.[1] Tazobactam can inhibit class A beta-lactamases but not class B.[4]

Another important resistance mechanism is the drug's inability to penetrate its site of action, with the outer membrane of Gram-negative bacteria serving as a barrier for this purpose. These microorganisms contain beta-lactamases in the periplasm between the outer cytoplasmic membrane and the outer lipopolysaccharide membrane, a strategy chosen to keep PBPs away from beta-lactam antibiotics. However, there are porins that allow the passage of molecules through this barrier depending on size, structure, and charge. Antibiotics that meet these requirements can pass through and bind to PBPs, but the absence or deletion of an essential porin, often associated with beta-lactamase activity, can lead to possible antibiotic resistance. Efflux is a third mechanism in which the drug that enters the periplasmic space is expelled from the membrane before it can act on PBPs. Usually, this efflux mechanism is accompanied by the destruction of antibiotics by beta-lactamases.[1] The primary mechanism that confers resistance to piperacillin-tazobactam is resistance due to structural differences in PBPs.[4] The action of PBPs in cell wall synthesis and assembly is essential, and the low affinity of PBPs

for beta-lactam antibiotics allows the antibiotic's effectiveness to be circumvented. This form of resistance occurs either through mutations in PBP genes that reduce binding affinity or through the presence of an additional low-affinity PBP.[1]

Spectrum

Piperacillin is a broad-spectrum antibiotic with effectiveness against strains of *Streptococcus* spp, *Neisseria* spp, *Haemophilus* spp, and other microorganisms in the *Enterobacteriaceae* family, such as *Klebsiella* spp, *Enterobacter* spp, *Serratia* spp, and indole-positive *Proteus*.[1,2] Additionally, it has an effective response against anaerobic cocci and bacilli and can inhibit approximately 60 to 90% of *Pseudomonas aeruginosa* strains at concentrations below 16 micrograms/ml. However, it is hydrolyzed by beta-lactamases of classes A and B, and it is often combined with tazobactam to enhance effectiveness against beta-lactamase-producing organisms.[1] The combination of piperacillin-tazobactam demonstrates in vitro antibacterial activity against *Escherichia coli* and *Klebsiella pneumoniae* producing ESBL, although it is less potent against ESBL-non-producing isolates. In clinical practice, bacteria such as *Enterobacter* sp, *Citrobacter* sp, *Burkholderia* sp, *Salmonella* sp, and *Stenotrophomonas maltophilia* are resistant to piperacillin-tazobactam.

Main clinical uses

Due to its activity against enterobacteria, anaerobes, and enterococci, piperacillin-tazobactam is indicated in Brazil for surgical intra-abdominal infections and hospital-acquired infections caused by *P. aeruginosa, Acinetobacter, Serratia, Klebsiella*, and indole-positive *Proteus*.[2,5] For the treatment of skin and soft tissue infections, pneumonia, intra-abdominal infections, polymicrobial infections, and febrile neutropenia in combination with an aminoglycoside, it demonstrates efficacy equal to or greater than antibiotics with a similar spectrum.[1] However, recent studies have concluded that empirical treatment with piperacillin-tazobactam is not recommended, which was also observed in infections caused by #P. aeruginosa#.[3,17,18,19] Regarding empirical use for patients with hospital-acquired sepsis and unknown-source septic shock, a study in Australia recognized a lack of more robust evidence for this recommendation.[17] Furthermore, the same study rejected the recommendation of piperacillin-tazobactam over carbapenems for ESBL producers, which was also certified in other reviews that even mention the reduced effectiveness of piperacillin-tazobactam when associated with carbapenem resistance.[3,17,18,19] Evidence exists for the use of piperacillin-tazobactam in the treatment of urinary tract infections caused by ESBL-producing *Enterobacteriaceae* if susceptibility is confirmed. However, the most appropriate approach for the treatment of ESBL-producing microorganism infections is conducting tests to identify resistance patterns and susceptibility to guide the best therapy.[6,7]

The use of antibiotics for the empirical treatment of *Pseudomonas* spp infections is risky and uncertain, and the use of piperacillin-tazobactam is not recommended due to the increasing resistance rates, according to a recent study. Therefore, rapid detection of resistance patterns and susceptibility to antimicrobials should be prioritized.[20] Of course, as we are dealing with severe infections potentially life-threatening, treatment should always be initiated based on monitoring the presumed sensitivity/resistance profiles of the agent and adjusted later based on culture results.

As previously mentioned, piperacillin is widely used in a hospital environment due to its effectiveness in infections that typically affect patients in these settings. However, this presents another challenge since critically ill patients require specific treatment due to physiopathological

changes that impact pharmacokinetics and cause variability in treatment effectiveness.[6,21] In such cases, there are good indications for continuous infusions and therapeutic drug monitoring, but further studies are needed to recommend this practice.[6]The required doses in critically ill patients are a challenge, and it is essential to achieve pharmacokinetic and pharmacodynamic goals. One study showed that defining these goals had more impact on the likelihood of achieving the target than the use or intensity of continuous renal replacement therapy, and it is necessary to define soft or more stringent targets, or even individualized goals depending on the patient.[21]

Adverse effects

Like most penicillins, hypersensitivity reactions are described, ranging from rash to anaphylaxis, superinfections, neurological toxicity at high doses, and irritative effects on blood vessels leading to phlebitis. In long-term administration at high doses, neutropenia may occur, which is reversible upon drug withdrawal. Less frequently, hypokalemia and changes in bleeding time occur.[1,2,16] Despite drug-related fixed drug eruptions being widely described in association with piperacillin-tazobactam, a recent case of generalized fixed drug eruption was published, which appears to be related to drug re-exposure.[7] In addition, specific dosing helps reduce adverse effects, while overexposure to piperacillin-tazobactam seems to be associated with increased mortality.[17,21]

It should be emphasized that the action of the drug against anaerobes can, collaterally, determine colonization by multi-resistant microorganisms, particularly when in a hospital environment. The intestinal microbiota is predominantly formed by such agents and, therefore, we can result in the emergence of multidrug-resistant infections, including fungal infections such as *Candida* spp.[22]

Conclusions

The antibiotic piperacillin-tazobactam is routinely used, primarily in situations that require decisive decisions, and a comprehensive and up-to-date understanding of the drug can assist in the therapeutic choices made on a daily basis. The safe use of the antibiotic for infections now depends on rapid testing of resistance and susceptibility to antimicrobials, and the empirical use of piperacillin-tazobactam or its use for ESBL-producing microorganisms is not recommended. In situations involving patients with renal replacement therapy, it is important to quickly achieve appropriate antibiotic goals, which require pre-determined targets. For critically ill patients, being aware of pharmacodynamic and pharmacokinetic variability is essential. However, several studies used in the construction of this article revealed the need for further research in clinical practice to address doubts and provide certainties, such as the indication for continuous therapy. Furthermore, the growing concern about antibiotic resistance underscores the need to consider alternatives, for example, to the currently used carbapenem. Although current studies indicate that piperacillin-tazobactam may not be the best alternative for all situations in critical patient care, new studies and new needs may determine new paths in this story.

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