RMMG
Revista Médica de Minas Gerais

REVIEW ARTICLE

Penicillins: update for clinical practice

Penicilinas: atualização para a prática clínica

Rodrigo Siqueira-Batista[1,2], Marcos Mauricio Reis Alves[1], Márcio Antônio Gaspar Lara[1], Andréia Patrícia Gomes[2], Jorge Luiz Dutra Gazineo[3], Luciene Muniz Braga[2]

ABSTRACT

Introduction: The discovery of penicillins is one of the milestones in the history of health care. These drugs are among the most prescribed antimicrobials in the world, with applicability even today in different diseases and infectious complications. **Objective:** To review the main pharmacological and therapeutic aspects of penicillins, with emphasis on the clinical use of these drugs. **Methods:** Narrative literature review directed at updating the most relevant pharmacological and therapeutic aspects of penicillins: (1) history; (2) mechanisms of action and bacterial resistance; (3) penicillins and immunomodulation; and (4) classification of antimicrobials. Results: The identification of penicillin G by Alexander Fleming in 1928 inaugurated the "Age of Antibiotics". The drugs are beta-lactams and therefore act on penicillin-binding proteins (PBPs), preventing the proper formation of peptidoglycans, which produces osmotic lysis of bacterial cells. Immunomodulatory properties of the drugs are described, the relevance of which still remains controversial. The classification of drugs allows the following groups to be distinguished: natural penicillins, aminopeniclins, isoxazolylpenicillins, carboxypenicillins, and ureidopenicillins. **Conclusion:** Penicillins continue to be important drugs today. The prescriber should act in accordance with the assumptions of the rational use of antimicrobials, which contributes to reducing the risk of developing bacterial resistance, a phenomenon that has acquired, in recent decades, tragic contours in different parts of the world.

Keywords: Anti-Bacterial agents; Drug resistance, bacterial; Penicillin; Penicillin-Binding proteins.

[1] School of Medicine, Faculdade Dinâmica do Vale do Piranga (FADIP), Ponte Nova, Minas Gerais, Brazil.

[2] Department of Medicine and Nursing, Universidade Federal de Viçosa (UFV), Viçosa, Minas Gerais, Brazil.

[3] Clementino Fraga Filho University Hospital, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil.

Responsible Editor:

Dr. Enio Roberto Pietra Pedroso

Faculty of Medicine of the Federal University of Minas Gerais

Belo Horizonte, MG, Brazil.

Corresponding Author:

Rodrigo Siqueira-Batista

E-mail: rsbatista@ufv.br

Institution that research was developed:

Faculdade Dinâmica do Vale do Piranga (FADIP); Universidade Federal de Viçosa; Universidade Federal do Rio de Janeiro.

Supporting sources:

There was no supply of equipment, materials or medicines.

Ethics Committee:

This job is not in of research definitions involving human beings. There is no need appreciation by the Ethics Committee.

RESUMO

Introdução: A descoberta das penicilinas é um dos marcos da história do cuidado à saúde. Tais medicamentos estão entre os antimicrobianos mais prescritos no mundo, com aplicabilidade, ainda hoje, em distintas enfermidades e complicações infecciosas. **Objetivo:** Descrever os principais aspectos farmacológicos e terapêuticos das penicilinas, com ênfase no uso clínico desses fármacos. **Métodos:** Revisão narrativa da literatura dirigida à atualização dos mais relevantes aspectos farmacológicos e terapêuticos das penicilinas: (1) histórico; (2) mecanismos de ação e resistência bacteriana; (3) penicilinas e imunomodulação; e (4) classificação dos antimicrobianos. **Resultados:** A identificação da penicilina G por Alexander Fleming, em 1928, inaugura a "Era dos Antibióticos". Os fármacos são beta-lactâmicos e, por conseguinte, agem sobre as proteínas ligadoras de penicilina (PBPs), impedindo a adequada formação de peptidoglicanas, o que produz lise osmótica das células bacterianas. São descritas propriedades imunomoduladoras dos medicamentos, cuja relevância ainda permanece controversa. A classificação dos fármacos permite distinguir os seguintes grupos: penicilinas naturais, aminopeniclinas, isoxazolilpenicilinas, carboxipenicilinas e ureidopenicilinas. **Conclusão:** As penicilinas seguem como importantes medicamentos na atualidade. O prescritor deve atuar em concordância com os pressupostos do uso racional de antimicrobianos, o que contribui para reduzir o risco de desenvolvimento de resistência bacteriana, fenômeno que tem adquirido, nas últimas décadas, trágicos contornos em diferentes partes do mundo.

Palavras-chave: Antibacterianos; Farmacorresistência bacteriana; Penicilinas; Proteínas de ligação às penicilinas.

Clinical trial registration:
Not applicable.

Conflict of interests:
The authors declare that they have no conflict of interests.

Received on: May 10, 2022
Approved on: January 25, 2023
Publication Date: August 31, 2023.

DOI: 10.5935/2238-3182.2023e33209-en

Introduction

The description of the antibacterial action of penicillin G was one of the most important contributions of science in the sphere of world health[1]. From this inaugural event, investments in research in the field of antimicrobial therapy were allocated in the first half of the 20th century, leading later to the identification of other classes of antibiotics. In medical literature, there are reports of its antibacterial action in the late 19th century, such as those by John Tyndall (1875) and Ernest Duchesne, (1897), related to the effect of *Penicillium glaucum* on certain bacteria[1,2].

However, it was only in 1928 that the Scottish scientist Alexander Fleming, researching strains of bacteria of the genus *Staphylococcus*, observed that the culture plates had been accidentally contaminated by a fungus of the genus *Penicillium*, which prevented bacterial growth. In 1940, Ernst Boris Chain and Howard Walter Florey proved their antibacterial action in humans, awarding the three scientists the 1945 Nobel Prize in Medicine and Physiology. The discovery of penicillins led to a revolution in the treatment of several infectious diseases and complications, for which there was still no specific therapy at the time, thus revolutionizing medicine, boosting the pharmaceutical industry and representing a watershed in the history of health sciences: the before and the after the advent of these drugs[1,2]. It is noteworthy that since then antimicrobials started to figure among the most prescribed drugs in the world, which can also be observed in Brazil, where they represent about 40% of the drugs used in clinical practice[2].

For almost a century, penicillins have been antimicrobials used in health care with satisfactory results, contributing to saving millions of lives during this period, and therefore should be considered much more than a mere scientific discovery[2]. These drugs - classified as natural and semisynthetic[3] - are considered the antibiotics of choice for prophylaxis of rheumatic fever recurrence, prophylaxis of lower limb erysipelas recurrence, prophylaxis of infections caused by *Haemophilus influenzae* and *Streptococcus pneumoniae* in children under five years with anatomical

or functional asplenia (including sickle cell anemia) or agammaglobulinemia, prophylaxis of infective endocarditis in dental procedures in high-risk patients, prophylaxis of early neonatal infections caused by *Streptococcus agalactiae* in pregnant women in labor less than 37 weeks or colonized (urine and/or anal *swab* and/or vaginal *swab*) by *S. agalactiae* or with rupture of membranes with ≥18 hours or with fever (≥38ºC) intrapartum, prevention of outbreaks of infections caused by *Streptococcus pyogenes* (group A), especially in military personnel in training program, treatment of infections caused by *S. pyogenes* and *S. agalactiae*, treatment of infective endocarditis caused by highly penicillin-sensitive strains of *Streptococcus gallolyticus* (*bovis*) and *Streptococcus viridans*, treatment of infections caused by *Eikenella corrodens*, *Listeria monocytogenes* and methicillin-susceptible *Staphylococcus aureus*, treatment of syphilis (primary, secondary or tertiary), therapy of otitis media, treatment of actinomycosis, therapy of severe forms of leptospirosis, among others[4-12]. *Mycoplasma* spp., *Chlamydia* spp., *Legionella* spp., *Rickettsia* spp. and fungi are microorganisms considered intrinsically resistant to penicillins[7].

The World Health Organization (WHO) stated in 2017 that bacterial resistance to antimicrobials is a major health problem worldwide and that inappropriate prescriptions are its main cause[13]. Also according to the WHO, bacteria such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Escherichia coli* are classified as critical priority for resistance, also highlighting the urgency for the discovery of new drugs with activity against these pathogens[14]. It should be noted that, currently, about 50% of all antibiotic prescriptions are for the treatment of an upper airway infection (UAI)[15]. Penicillins are among the most commonly used antimicrobials for this purpose, although recent studies indicate that 30 to 50% of antibiotic prescriptions are inappropriate[16,17].

Based on these preliminary considerations, the purpose of this article is to review the main aspects of penicillins, emphasizing their use in everyday clinical practice.

METHODS

This manuscript, from a methodological point of view, represents a narrative literature review – which "*describes and discusses the state of the science of a specific topic or theme from a theoretical and contextual point of view*" (Botelho et al., 2011, p. 125)[18], in terms of its "*fundamental role for continuing education*" (Rother, 2007, p. v)[19] by allowing the "*reader to acquire and update knowledge on a specific theme in a short period of time*" (Rother, 2007, p. v)[19] – with a view to updating the main pharmacological and therapeutic aspects of penicillins. Thus, unlike a systematic review – which aims to "*answer a specific question about a specific health problem*" (Ercole et al., 2014, p. 9,10)[20] – the bibliographic research undertaken here is appropriate to "*describe and discuss the development or the 'state of the art' of a given subject from a theoretical or contextual point of view*" (Rother, 2007, p. v)[19].

In effect, references – articles, books, and documents published by governmental bodies and scientific societies – were sought from the authors' knowledge, and critically analyzed. The selected manuscripts were read in their entirety to extract the most relevant data. The information obtained – in texts published in English, Spanish and Portuguese – allowed the organization of the following topics, which constituted the essential elements addressed in the Results and Discussion: (1) historical aspects of the description of the drugs; (2) mechanisms of action and bacterial resistance; (3) penicillins and immunomodulation; and (4) classification of antimicrobials.

Results and Discussion

Brief history

The investigations developed by Robert Koch and Louis Pasteur were used by several scholars during the 20th century for the development of the "Germ Theory", which made possible the association of microorganisms with well-known diseases. This allowed the search for specific drugs for the treatment of these nosological entities, demanding attention from the scientific community since the turn of the 19th to the 20th century. However, it can be considered, in a way, that it was chance that changed the course of antimicrobial treatment[1,2].

In 1928, scientist Alexander Fleming was working in the laboratory of St. Mary's Hospital in London. Returning from vacation, he observed a Petri dish where something prevented bacterial growth. It was later found that it was caused by a fungus belonging to the genus *Penicillium*, whose species was formerly known as *Penicillium notatum,* and is now known as *Penicillium chrysogenum*[21]. Thus, almost a century ago, Fleming's discovery started a radical change in the directions of medicine. However, only two decades after its description, penicillin was produced in large scale, being used in the treatment of wounds of the "allied" soldiers in the Second World War[1,2].

The description of penicillin then produced the beginning of the "Age of Antibiotics"; unfortunately, each discovery was consistently followed by the emergence of antimicrobial resistance[21]. Originally, *Staphylococcus aureus* was very sensitive to penicillin, but the frequency of resistant *S. aureus* strains in hospital settings increased during the period 1942 to 1958, reaching a value of over 70% of all isolates. The resistance was due to the production of beta-lactamases (penicillinases), enzymes that rapidly hydrolyze penicillin, and this phenomenon was mediated by plasmid conjugation[7]. In 1961, the first methicillin-resistant strain of *S. aureus* – and, by extension, considered resistant to all beta-lactam antibiotics, including cephalosporins, monobactams, and carbapenems – was identified in the United Kingdom[22]. This opens a *new chapter* in microbial resistance to antibiotics, as will be discussed below.

Mechanism of action and bacterial resistance

Bacteria have several components in their cell wall, especially peptidoglycan, whose function is to promote rigid mechanical stability in bacteria. Penicillins, like other beta-lactams (cephalosporins, carbapenems, and monobactams), have the beta-lactam ring in their chemical structure. These drugs bind to penicillin *binding* proteins (PBPs), which are present in the cell membrane of bacteria. This process prevents the last step of peptidoglycan formation, causing osmotic lysis of the bacterial cells, thus resulting in a bactericidal action on susceptible bacteria[8].

Antimicrobial resistance is a natural phenomenon, but it becomes a worrisome problem when it is accelerated by the incorrect use of such drugs[14]. The indiscriminate and excessive use of antimicrobials in the community, in hospitals, or even in animal husbandry, has directly contributed to the development of bacterial resistance, raising treatment costs, reducing the available therapeutic options, and determining prolonged hospitalization of patients, further increasing morbidity rates[22,23].

Bacterial resistance can occur by several mechanisms, either intrinsic or acquired. Intrinsic resistance occurs naturally, by means of biological aspects inherent to microorganisms. Acquired resistance, on the other hand, emerges from the selective pressure exerted by the indiscriminate use of antimicrobials, and may come from genetic mutations, originating resistance genes that can be transferred among bacterial species[23-25]. Bacteria can have intrinsic resistance or acquire resistance to beta-lactam antibiotics by four main mechanisms: (a) altered affinity of the drug for PBPs, (b) inability of the drug to reach the site of action due to changes in the outer membrane, (c) production of beta-lactamases that inactivate penicillins (penicillinases), and (d) efflux of the drug across the outer membrane of Gram-negative bacteria[23,26].

Penicillins and immunomodulation

Penicillins, like other antimicrobials, act on the viability and growth of pathogenic bacteria as their action mechanism. However, studies have shown that in addition to its bactericidal activity, there is an immunomodulatory action[27-29]. The therapeutic relevance of these properties is still controversial[30]. This activity occurs by inhibiting the release of pro-inflammatory cytokines – such as IL-1β, IL-6, IL-8 – and consequently, there is a reduction in the inflammatory response.

Beta-lactam antibiotics have the ability to activate GLT-1 (glutamate transporter) expression in astroglial cells thereby capturing excess glutamate in the synaptic cleft, and delivering it inside the astrocytes where it is converted back to glutamine[31]. Dysregulation in glutamate transport is involved in the pathogenesis of several neurological diseases such as stroke, epilepsy, multiple sclerosis, Alzheimer's disease, Parkinson's disease, among others[32].

Another immunomodulatory effect induced by penicillins was described by por Lee et al. (2016)[33]. In this study, it was demonstrated that mice pretreated for five days with ampicillin showed less neuronal damage when placed under transient global ischemia of the forebrain. Apparently this result was due not only to the activation of GLT1, but also to the attenuation of immunoreactivity that cellular hypoxia produces[34].

Studies have shown that penicillin derivatives have anti-inflammatory activity in patients with rheumatic fever, thus acting on the differentiation of human T lymphocytes[29]. Several studies have also demonstrated the immunomodulatory action of antimicrobials, especially among macrolides and tetracyclines. However, recent studies show that, in the group of penicillins, there are antibiotics with potentially neuroprotective, antioxidant, analgesic or immunomodulatory actions[27]. Due to these immunomodulatory actions, antibiotics called "immunosuppressive" have shown promise in the treatment of inflammatory or autoimmune diseases[30].

Penicillins classification

1. "Natural" penicillins

The so-called natural penicillins include the G penicillins (Crystalline, Procaine and Benzathine) and penicillinV[1,2].

- Crystalline Penicillin G, given intravenously (IV): in adults 2 to 4 million units every 4 hours; in children 300,000 units/kg/day, divided into 6 doses[34].

- Penicillin G procaine, given intramuscularly (IM), 12 to 24 hours: in adults 600,000 to 1 million units/per day; in children 50,000 units/kg per day[34].

- Penicillin G benzathine, given by IM as a single weekly dose: in adults 1.2 to 2.4 million units; in children 50,000 units/kg[34].

- Penicillin V, given orally (30 minutes to 2 hours before meals): in adults 125 to 500mg, every 6 hours; in children 25 to 75mg/kg/day, divided into 3 to 4 doses.

The antimicrobial spectrum of natural penicillins encompasses *Actinobacillus actinomycetemcomitans*, *Actinomyces* spp., *Arachnia* spp., *Bacteroides melaninogenicus, Bacteroides oralis, Bacillus anthracis* and many other *Bacillus* spp. (except *B. cereus)*, *Bifidobacteria* spp, *Bordetella pertussis*, *Borrelia burgdorferi*, *Borrelia hermsii*, *Capnocytophaga canimorsus*, *Cardiobacterium hominis, Clostridium* (except some strains of *C. perfringens, C. tertium, and C. butyricum*), *Corynebacterium diphtheriae* and many other corynebacteria (except JK), *Eikenella corrodens, Erysipelothrix rhusiopathiae*, *Eubacterium* spp, *Fusobacterium necrophorum, Fusobacterium nucleatum*, *Haemophilus influenzae* (non-beta-lactamase producing strains), *Kingella kingae/indologenes, Lactobacilli* spp., *Leptospira* spp., *Leuconostoc* spp., *L. monocytogenes*, *Moraxella* spp. (not *catarrhalis*), *Neisseria lactamica*, *Neisseria meningitidis* (but with reduced sensitivity to penicillin in some countries, including Brazil), *Pasteurella multocida*, *Peptococci* spp. and anaerobic *Streptococcus, Prevotella melaninogenica*, *Propionibacterium* spp., *Spirillum minus*, *Streptobacillus moniliformis*, Streptococcus *agalactiae, Streptococcus pneumoniae* (except intermediate and high level resistance

strains), Streptococcus *pyogenes* (group A), *Streptococcus* spp. (alpha and beta hemolytic), *Treponema pallidum*, *Veillonella* spp.[7]. Among the methicillin-susceptible strains of *S. aureus*, up to 25% are also susceptible to penicillin[35-38].The use of penicillin in the treatment of penicillin-susceptible *S. aureus* infections may result in improved clinical outcomes for patients[35,38]. However, in these cases, clinicians should consider requesting a test to detect the production of penicillinases[35,37].

Benzathine penicillin G is the treatment of choice for patients with syphilis and should be given one week apart in the treatment of late latent syphilis, when three weekly doses of 2,400,000U are given intramuscularly[21]. Results of a recent systematic review support the use of penicillin in neonates with possible, highly probable, or confirmed congenital syphilis. High- and moderate-quality evidence suggests that there is probably no difference between penicillin G benzathine and penicillin G procaine regarding the outcomes of absence of clinical manifestations of syphilis or serological cure in newborns with congenital syphilis[38]. The treatment of choice for neurosyphilis is crystalline penicillin G[39,42]. Other clinical indications for the use of benzathine penicillin G are: treatment of pharyngitis due to *S. pyogenes*, prophylaxis of rheumatic fever and alternative therapy for asymptomatic carriers of *C. diphtheriae*[43,44] . There is no evidence that *S. pyogenes* has become resistant to penicillin over the years[45,46].

The main adverse event after the use of penicillin G is hypersensitivity; many patients report being allergic to penicillin, but few have clinically significant reactions (less than 5%)[39]. Morbilliform exanthema, fever, eosinophilia, interstitial nephritis, contact dermatitis, hemolytic anemia (in very high doses administered intravenously), Jarisch-Herxheimer reaction (usually limited to treatment of syphilis or leptospirosis), and seizures (especially in patients with renal dysfunction) can occur. Less frequently myoclonus, paresthesia, hyperreflexia, and coma may occur[7,8].

Penicillin V has a similar antimicrobial spectrum to penicillin G, but it is 5 to 10 times less active against *Neisseria* spp., *Haemophilus* spp. and some anaerobes. Its use is preferable to that of benzathine penicillin G for rheumatic fever prophylaxis in patients with severe heart disease, since cases of vasovagal collapse have been reported after prophylactic use of benzathine penicillin G in these patients[47] Its adverse effects are similar to those of penicillin G, except that there are no neurological disorders. An important difference between penicillin G and penicillin V is that penicillin V is more stable at acidic pH, and thus better absorbed in the gastrointestinal tract[34].

2. Aminopenicillins

These are semisynthetic penicillins, in which an amino grouping has been added to the side chain, thus increasing their spectrum of action in relation to natural penicillins and with parenteral or oral routes of administration[24]. Among the drugs that belong to this group are bacampacillin, cyclacycline, epicycline, hetacycline, lenampicillin, metampicillin, pivampicillin, thalampicillin, amoxicillin, and ampicillin, the last two being used in Brazilian medical practice[1,2].

Ampicillin can be given orally or parenterally, and its usual dose ranges from 50 to 100mg/kg/day orally every 6 hours, or 50 to 300mg/kg/day IM or IV every 6 hours. In the treatment of meningoencephalitis caused by susceptible bacteria, the usual dose is 200 to 400mg/kg/day, IV every 4 to 6 hours (maximum of 12 grams/day)[3,47]. The spectrum of ampicillin's action includes *Streptococcus* spp., *Enterococcus* spp. (more active *in vitro* than penicillin G), *L. monocytogenes* (more active *in vitro* than penicillin G); *E. corrodens*, some enteric Gram-negatives (*Salmonella* spp., *Shigella* spp. and *Proteus mirabilis*), *H. influenzae* (non-beta-lactamase producer)[8,34]. It should not be used in the treatment of *S. aureus* infections, as it is often inactivated by the penicillinase produced by this bacterium. It has limited *in vitro* activity against anaerobic bacteria. It is inactive against *Pseudomonas* spp., *Citrobacter* spp., *Serratia* spp., *Enterobacter* spp., *Providencia* spp. and *Acinetobacter* spp.[503].

Adverse reactions include hypersensitivity, transient increase in aminotransferases, interstitial nephritis, thrombocytopenia, and when used orally, gastrointestinal adverse events such as diarrhea, nausea, and vomiting.

Amoxicillin is administered orally, with the usual dose being 30 to 50mg/kg/day every 8 hours. For adults the recommended dose is 0.5 to 1 g every 8 to 12 hours, although doses of up to 1 g every 4 hours have been used6. Its action spectrum includes *Streptococcus* spp.. *Enterococcus* spp., *L. monocytogenes,* some enteric Gram-negative (*Salmonella* spp.), *H. influenzae* (non-beta-lactamase producing) and *Helicobacter pilori*. Compared to ampicillin, amoxicillin is twice as active *in vitro* against *E. faecalis* and *Salmonella* spp. but twice as less active *in vitro* against *Shigella* spp.[7,8,48].

The main adverse reactions of amoxicillin are similar to those of ampicillin, but it has better oral absorption than ampicillin (74 to 92%), due to its greater stability in acidic pH, and is therefore more appropriate than ampicillin in the sequential therapy of parenterally administered penicillins (penicillin G or ampicillin)[40,50].

Ampicillin and Amoxicillin are inactivated by beta-lactamases present in both Gram-negative and Gram-positive bacteria. Thus, a combination of these drugs with beta-lactamase inhibitors, which inhibit the action of beta-lactamases and prevent the destruction of antibiotics by these enzymes, becomes necessary. The beta-lactamase inhibitors currently available in clinical practice are clavulanic acid, sulbactam, tazobactam, avibactam, relebactam, and vaborbactam, the first two of which are combined with the aminopenicillins[25,51]. Zidebactam and nacubactam are currently under investigation in clinical trials[51].

Amoxicillin/clavulanic acid can be given orally and parenterally, with the usual oral dose of amoxicillin being 30 to 50mg/kg/day, every 8 or 12 hours, or 30 to 100mg/kg/day IV amoxicillin, every 6 or 8 hours, having the same adverse reactions as amoxicillin. *Citrobacter freundii, Enterobacter cloacae, Hafnia alvei, Klebsiella aerogenes,*

Morganella morganii, Plesiomonas shigelloides, Providencia rettgeri, Providencia stuartii, Serratia marcescens, Yersinia enterocolitica, Aeromonas hydrophila, Aeromonas veronii, Aeromonas dhakensis, Aeromonas caviae, and *Aeromonas jandaei* generally exhibit intrinsic resistance to amoxicillin/clavulanic acid. Furthermore, it is inactive against *Pseudomonas* spp. and methicillin-resistant *S. aureus (*MRSA)[48,50]. It should be noted that two nationwide, retrospective cohort studies conducted in the United States have shown amoxicillin/clavulanic acid to be effective in the outpatient treatment of diverticulitis, with the added benefit of reducing the risk of pseudomembranous colitis, when compared with treatment with metronidazole and fluoroquinolone[52].

Ampicillin/sulbactam is administered IV with a usual dose of 50 to 150mg/kg/day of ampicillin every 6 hours. Ampicillin-sulbactam is an option to treat infections caused by *Acinetobacter calcoaceticus* and *A. baumannii* complex (including carbapenem-resistant strains)[51,53-57], despite the fact that increasing antimicrobial resistance of *Acinetobacter* spp. has been reported in Brazil[55]. Ampicillin/sulbactam is not active *in vitro* against *P. aeruginosa* and MRSA[52].

Amoxicillin/sulbactam has the same spectrum of action as the above combinations, is administered orally or parenterally, at the usual dose of 30 to 50mg/kg/day amoxicillin VO or IV, every 8 hours, and has the same adverse reactions as amoxicillin. This combination has a lower *in vitro* activity against *A. baumanni* than ampicillin/sulbactam[56].

An experimental study of *Bacillus anthracis* meningitis in rabbits demonstrated the efficacy of combining ampicillin or amoxicillin with a beta-lactamase inhibitor in treating this infectious condition, compared to treatment with meropenem or piperacillin[60].

In the prophylaxis or treatment of infections associated with dog, cat, or human bites, generally a beta-lactam associated with a beta-lactamase inhibitor-such as oral amoxicillin/clavulanic acid (or ampicillin-sulbactam, if intravenous therapy is indicated)-is the treatment of choice. Such a combination has in *vitro* activity against the main etiologic agents of these infections: *P. multocida*, *E. corrodens*, *Streptococcus* spp. anaerobes and *S. aureus* (non MRSA)[44,61].

3. Antistaphylococcal drugs (isoxazolylpenicillins)

The isoxazolylpenicillins are semisynthetic analogues of penicillin, which show high resistance to cleavage by penicillinase, and are represented by cloxacillin, dicloxacillin, flucloxacillin, oxacillin, methicillin, and nafcillin[1,2].

Methicillin was the first antistaphylococcal penicillin to be produced, and it presented an important resistance to the action of beta-lactamases of *S. aureus* strains. However, in the early 1960s, bacteria resistant to this antimicrobial appeared. Its use was discontinued until it was no longer used in medical practice due to nephrotoxicity, being then replaced mainly by oxacillin, dicloxacillin and flucloxacillin[8]. Its importance is now historical; with the name methicillin-resistant strains of *S. aureus* (MRSA)[1,2].

Oxacillin is the most commonly used isoxazolylpenicillin; its only route of administration is IV, with a dose that can vary from 100 to 200mg/kg/day, up to a maximum of 12g/day, divided in intervals of 4 or 6 hours. Its spectrum of action includes methicillin-sensitive strains of *S. aureus* and *Staphylococcus epidermidis, Streptococcus* spp. (except penicillin-resistant *S. pneumoniae*), and is inactive against *Enterococcus* spp., *L. monocytogenes,* enterobacteriaceae, *Neisseria gonorrhoeae* and *B. fragilis*[8,34]. Oxacillin is more effective than vancomycin in treating patients with infections caused by methicillin-susceptible *S. aureus*[39,61]. The primary indication for oxacillin is treatment of *S. aureus* (methicillin-sensitive) infections from the community[1,2].

The main adverse reactions to oxacillin are hypersensitivity reactions, hepatitis (mainly associated with prolonged use of the antibiotic), interstitial nephritis, and leukopenia[8] (the latter can eventually assume marked severity).

4. Carboxypenicillins

Described in 1965, the class includes carbenicillin, the first penicillin with anti-Pseudomonas activity. The main drugs are carbenicillin, carfecillin, carindacillin, and ticarcillin. They are semisynthetic penicillins and inactivated by beta-lactamases, and have a mechanism of action similar to that of penicillin G[1,2].

Carbenicillin, as one of the main representatives of the carboxyenicillins group, has a spectrum of action, in general terms, Gram-positive germs sensitive to penicillin G (however it is less active than this drug) and Gram-negative germs such as *P. aeruginosa*, *Proteus* spp., *Enterobacter* spp., *Acinetobacter* spp. and *Serratia* spp. It is used at the usual dose of 100 to 500mg/kg/day, IV, every 1, 2 or 4 hours. Among the side effects are: hypersensitivity, coagulation disturbances (platelet dysfunction), drug hepatitis, and convulsions (in patients with chronic renal failure), besides the risk of sodium overload. It is a drug that is practically inactive against *Klebsiella* spp. and inactive against beta-lactamase-producing *Enterococcus* spp., *S. aureus*, *Haemophilus* spp. and beta-lactamase-producing *N. gonorrheae* and *Moraxella*[8].

Another important representative of the carboxyenicillins is ticarcillin, which in its pharmacological presentation available in Brazil includes the association with clavulanic acid (beta-lactamase inhibitor). Its spectrum of action includes methicillin-sensitive *S. aureus*, *Streptococcus* spp., Gram-negative (including *Klebsiella* spp., *Enterobacter* spp. *and P. aeruginosa*), anaerobes (including many strains of *B. fragilis*). It is used in children at a dose of 200 to 300mg/kg/day, IV, every 6 hours (in neonates - 200mg/kg/day, IV, every 6 hours) and in adults 3.1g/dose, IV, every 4 to 6 hours. Side effects include hypersensitivity, coagulation disorders (platelet dysfunction), hypokalemia, sodium overload, drug hepatitis, and seizures. It is important to note the inactivity of the drug against *Enterococcus* spp. and MRSA[8].

Currently ticarcillin, carbenicillin, and indanyl carbenicillin (carbenicillin ester used for oral administration) are no longer used in clinical practice in the US because of the large doses required, the greater potential for toxicity, and the availability of more potent therapeutic alternatives[34].

Furthermore, none of the carboxypenicillins are included in the national list of essential drugs prepared by the Brazilian Ministry of Health[62].

5. Ureidopenicillins (anti-*Pseudomonas*)

The ureidopenicillins, also called by some authors fourth generation penicillins or extended spectrum penicillins, are semisynthetic antibiotics derived by adding a urea molecule to the ampicillin chain. It is a broad class of antibiotics with several representatives: alpacillin, aspoxicillin, azlocillin, furazlocillin, furbenicillin, mezlocillin, piperacillin, and pyrbenicillin. However, only piperacillin associated with tazobactam is used in Brazil[2]. Still within the ureidopenicillins, there are the sulfobezylpenicillins represented by sulbenicillin, sulfocillin, and suncillin.

In Brazil, piperacillin is associated with tazobactam (beta-lactamase inhibitor) and has a broad spectrum of action: methicillin-sensitive *S. aureus, Streptococcus* spp., *E. faecalis,* Gram-negative (including *Klebsiella* spp., *H. influenzae, M. catarrhalis, Yersinia enterocolitica* and *P. aeruginosa)*, anaerobes (including most strains of *B. fragilis*). Bacteria such as *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Salmonella* spp., and *Stenotrophomonas maltophilia* are mostly resistant to piperacillin/tazobactam. Furthermore, this antibiotic has no activity against vancomycin-resistant (VRE) strains of MRSA and *Enterococcus* spp[8,26,34].

Extended-spectrum beta-lactamase (ESBL)-producing strains of *E. coli* and *Klebsiella* spp. are often sensitive to piperacillin/tazobactam *in vitro*, but there has been some reluctance to use this antimicrobial since the possibility of therapeutic failure is high when other beta-lactam antibiotics, except carbapenems, are used to treat infections caused by these bacteria[63,64] .

It is generally used in adults at a dose of 4.5g (4.0g piperacillin/0.5g tazobactam), IV, in a prolonged infusion (3 to 4 hours), every 6 hours (if creatinine *clearance* is greater than 40ml/minute)[8,66,67]. It is safe and effective in children and neonates at a dose of 80mg/kg piperacillin dose and 10mg/kg tazobactam dose every 8 hours in children under 9 months and 100mg/kg piperacillin dose and 10mg/kg tazobactam dose every 8 hours in children over 9 months[68].

Adverse reactions may include gastrointestinal events (diarrhea and nausea), hypersensitivity reactions, seizures, mild hypokalemia, risk of bleeding (changes in platelet function are less common than with the carboxypenicillins)[8,26] and nephrotoxicity when given concomitantly with vancomycin (observed in a recent meta-analysis of prospective studies)[69].

Concluding Remarks

Antimicrobials in general – and penicillins in particular – are among the most prescribed drugs in the world and in Brazil, a context that increases the responsibility of professionals for their rational use in clinical practice, taking into account – especially – the indications, contraindications, impacts on microorganisms and adverse effects.

Pathogen resistance to antimicrobials is a phenomenon related to the – often indiscriminate – use of drugs in human and animal health. Indeed, there is a need for improved control and surveillance of anti-infective drugs, since the connectivity of natural and artificial ecosystems (e.g., agricultural, hospital and others) has a direct relationship with the emergence, evolution and spread of resistant germs. Thus, one of the interesting strategies to address the problem is the One Health approach, according to which the phenomenon of microorganism resistance to antimicrobials should be addressed in terms of the different interactions established within the environment, reducing the risk of global health threats[70-73].

Another important aspect regarding the use of penicillins concerns the hypersensitivity events (which have been commented on at different points in this article). The low risk of severe allergic reactions to the drugs and, especially, the inaccurate use of the term "allergy" by family members and health professionals in the daily prescription of antimicrobials should be emphasized. In these terms, there is a need for training of health care teams to differentiate between immunoglobulin E (IgE)-mediated hypersensitivity events, drug intolerances, and other idiosyncratic reactions that may occur days after exposure. Therefore, before discarding penicillins as an option – because of the hypothesis of prior allergy – it is necessary to perform a detailed anamnesis and an analysis of the risks and benefits of the option – or not – of prescribing a penicillin and possibly some other beta-lactam[2,8,40].

Based on these considerations, the present article sought to present information regarding the main penicillins used in Brazil for the treatment of infectious conditions. The reviewed elements may help, hopefully, in the choice of the most adequate antimicrobial, considering the concept of *ideal antibiotic* – according to Schechter (1998)[74] –, which gathers the following requirements be selective against microorganisms and have minimal toxicity to the patient; keep the saprophytic microbiota unaltered; not induce resistance in sensitive pathogens; have bactericidal action; maintain bioavailability in relation to the route of administration; be stable in solution and have a prolonged half-life; have excellent penetration into various organs, fluids and tissues; be highly effective regardless of local conditions such as pH and temperature; and finally, should have low cost[74].

The *ideal antibiotic*, of course, does not exist in the real world, but as a concept it allows prescribers to choose the drug that is most appropriate to the patient's needs. In this sense, the management of knowledge about penicillins is useful to assist the indication of these drugs – when they show themselves as the *most ideal antimicrobial possible* – minimizing the risks of their indiscriminate use, whose consequences, often disastrous, are the exposure of people to unjustifiable risks of adverse effects and selection pressure on bacteria, accentuating the already serious problem of bacterial resistance.

"*The young physician starts life with twenty drugs for each disease, and the old physician ends life with one drug for twenty diseases.*"
(*Sir* William Osler, 1903)[75].

Authors' Contributions

Rodrigo Siqueira-Batista, Main author; active participation in planning, data collection, completion and final review.

Marcos Mauricio Reis Alves, participation in data collection, writing, conclusion and final revision.

Márcio Antônio Gaspar Lara, participation in data collection, writing, conclusion and final revision.

Andréia Patrícia Gomes, participation in data collection, writing, conclusion and final revision.

Jorge Luiz Dutra Gazineo, participation in data collection, writing, conclusion and final revision.

Luciene Muniz Braga, participation in data collection, writing, conclusion and final revision.

Copyright

References

1. Brunton LL, Hilal-Dandan R, Knollmann BC. The Pharmacological Basis of Therapeutics by Goodman and Gilman. 13th ed. New York: Amgh Publishing; 2018.
2. Tavares W. Antibióticos e quimioterápicos para o clínico. 4th ed. São Paulo (SP): Editora Atheneu; 2020.
3. Siqueira-Batista R, Gomes AP, Gazineo JLD, Miguel PSB, Santana LA, Oliveira L, et al. Meningococcal disease, a clinical and epidemiological review. Asian Pac J Trop Med. 2017 Nov;10(11):1019-29.
4. Cahill TJ, Harrison JL, Jewell P, Okakpoya I, Chambers JB, Dayer M, et al. Antibiotic prophylaxis for infective endocarditis: a systematic review and meta-analysis. Heart. 2017 Jun;103(12):937-44.
5. Chambers HF, Bayer AS. Native-valve infective endocarditis. N Engl J Med. 2020;383(6):567-76.
6. Dalal A, Eskin-Schwartz M, Mimouni D, Ray S, Days W, Hodak E, et al. Interventions for the prevention of recurrent erysipelas and cellulitis. Cochrane Database Syst Rev. 2017;2017(6):CD009758.
7. Geddes A, Gould I, Roberts J, Grayson M, Cosgrove S. Ampicillin and Amoxicillin. In: Grayson LM, Cosgrove S, Crowe S, eds, et al. Kucers' the Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic and Antiviral Drugs. 7th ed. Boca Raton (FL): CRC Press; 2017.
8. Reese R, Betts R. Antibiotic use. In: Betts RF, Chapman SW, Penn RL, eds. Reese and Betts' a practical approach to infectious diseases. 5th ed. Lippincott Williams & Wilkins; 2003.
9. Rajani R, Klein JL. Infective endocarditis: a contemporary update. Clin Med (Northfield Il). 2020;20(1):31-5.
10. Webber BJ, Kieffer JW, White BK, Hawksworth AW, Graf PCF, Yun HC. Chemoprophylaxis against group A streptococcus during military training. Prev Med (Baltim). 2019;118:142-9.
11. Cober MP, Phelps SJ. Penicillin Prophylaxis in Children with Sickle Cell Disease. J Pediatr Pharmacol Ther. 2010;15(3):152-9.
12. Steer JA, Lamagni T, Healy B, Morgan M, Dryden M, Rao B, et al. Guidelines for prevention and control of group A streptococcal infection in acute healthcare and maternity settings in the UK. J Infect. 2012 Jan;64(1):1-18.
13. Harbarth S, Balkhy HH, Goossens H, Jarlier V, Kluytmans J, Laminarayan R, et al. Antimicrobial resistance: one world, one fight! Antimicrob Resist Infect Control. 2015;4(1):49.
14. Organização Mundial da Saúde (OMS). World health organization releases global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. J Med Soc. 2018;32(1):76-7.
15. Piltcher OB, Kosugi EM, Sakano E, Mion O, Testa JRG, Romano FR, et al. How to avoid the inappropriate use of antibiotics in upper respiratory tract infections? A position statement from an expert panel. Braz J Otorhinolaryngol. 2018;84(3):265-79.
16. McCullough AR, Pollack AJ, Hansen MP, Glasziou PP, Looke DF, Britt HC, et al. Antibiotics for acute respiratory infections in general practice: comparison of prescribing rates with guideline recommendations. Med J Aust. 2017 Jul;207(2):65-9.
17. Fleming-Dutra KE, Hersh AL, Shapiro DJ, Bartoces M, Enns EA, File Junior TM, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. JAMA. 2016 May;315(17):1864-73.
18. Botelho LLR, Cunha CCA, Macedo M. The integrative review method in organizational studies. Gestão e Soc. 2011;5(11):121.
19. Rother ET. Systematic review X narrative review. Acta Paul Enferm. 2007;20(2):v-vi.
20. Ercole FF, Melo LS, Alcoforado CLGC. Revisão integrativa versus revisão sistemática. Rev Min Enferm. 2014;18(1):9-10.
21. Alves MMR, Lara MAG, Gomes AP, Gazineo JLD, Braga LM, Castro ASB, et al. Penicilina G: atualização. Rev Saúde Dinâmica. 2022;12(3):66-89.
22. Jubeh B, Breijyeh Z, Karaman R. Resistance of Gram-positive bacteria to current antibacterial agents and overcoming approaches. Molecules. 2020;25(12):2888.
23. Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiol. 2018;4(3):482-501.

24. Agência Nacional de Vigilância Sanitária (BR). Módulo 3: Resistência Microbiana – mecanismo e impacto clínico. Brasília (DF): Anvisa; 2007.

25. Breijyeh Z, Jubeh B, Karaman R. Resistance of Gram-negative bacteria to current antibacterial agents and approaches to resolve it. Mol. 2020;25(6):1340.

26. Gin A, Dilay L, Karlowsky JA, Walkty A, Rubinstein E, Zhanel GG. Piperacillin-tazobactam: a β-lactam/β-lactamase inhibitor combination. Expert Rev Anti Infect Ther. 2007;5(3):365-83.

27. Ochoa-Aguilar A, Ventura-Martinez R, Sotomayor-Sobrino MA, Gómez C, Morales-Espinoza MR. Review of antibiotic and non-antibiotic properties of beta-lactam molecules. Antiinflamm Antiallergy Agents Med Chem. 2016;15(1):3-14.

28. Shams A, Asl A, Owlia S, Owlia M. Effects of crystalline penicillin G sodium on human T-cells differentiation. J Res Med Sci. 2021;26(1):19.

29. Brooks BM, Hart CA, Coleman JW. Differential effects of β-lactams on human IFN-γ activity. J Antimicrob Chemother. 2005;56(6):1122-5.

30. Labro MT. Immunomodulatory effects of antimicrobial agents. Part I: antibacterial and antiviral agents. Expert Rev Anti Infect Ther. 2012;10(3):319-40.

31. Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, et al. β-Lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature. 2005 Jan;433(7021):73-7.

32. Mehta A, Prabhakar M, Kumar P, Deshmukh R, Sharma PL. Excitotoxicity: bridge to various triggers in neurodegenerative disorders. Eur J Pharmacol. 2013;698(1-3):6-18.

33. Lee KE, Cho KO, Choi YS, Kim SY. The neuroprotective mechanism of ampicillin in a mouse model of transient forebrain ischemia. Korean J Physiol Pharmacol. 2016;20(2):185.

34. Doi Y. Penicillins and β-lactamase inhibitors. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier Saunders; 2020.

35. Butler-Laporte G, Lee TC, Cheng MP. Increasing rates of penicillin sensitivity in Staphylococcus aureus. Antimicrob Agents Chemother. 2018;62(7):e00680-18.

36. Cheng MP, Rene P, Cheng AP, Lee TC. Back to the Future: Penicillin-Susceptible Staphylococcus aureus. Am J Med. 2016;129(12):1331-1333.

37. Resman F, Thegerström J, Månsson F, Ahl J, Tham J, Riesbeck K. The prevalence, population structure and screening test specificity of penicillin-susceptible Staphylococcus aureus bacteremia isolates in Malmö, Sweden. J Infect. 2016;73(2):129-35.

38. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy. JAMA. 2019;321(2):188.

39. Henderson A, Harris P, Hartel G, Paterson D, Turnidge J, Davis JS, et al. Benzylpenicillin versus flucloxacillin for penicillin-susceptible Staphylococcus aureus bloodstream infections from a large retrospective cohort study. Int J Antimicrob Agents. 2019 Oct;54(4):491-5.

40. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Reports. 2021;70(4):1-187.

41. Walker GJ, Walker D, Molano Franco D, Grillo-Ardila CF. Antibiotic treatment for newborns with congenital syphilis. Cochrane Database Syst Rev. 2019;2019(2):CD012071.

42. Buitrago-Garcia D, Martí-Carvajal AJ, Jimenez A, Conterno LO, Pardo R. Antibiotic therapy for adults with neurosyphilis. Cochrane Database Syst Rev. 2019 May;5(5):CD011399.

43. Cots JM, Alós JI, Bárcena M, Boleda X, Canada JL, Gómez N, et al. Recomendaciones para el manejo de la faringoamigdalitis aguda del adulto. Enferm Infecc Microbiol Clin. 2016 Nov;34(9):585-94.

44. Nathwani D, Wood MJ. Penicillins. A current review of their clinical pharmacology and therapeutic use. Drugs. 1993 Jun;45(6):866-94.

45. Wessels MR. Streptococcal pharyngitis. N Engl J Med. 2011;364(7):648-55.

46. Sanyahumbi A, Ali S, Benjamin IJ, Karthikeyan G, Okello E, Sable CA, et al; American Heart Association. Penicillin Reactions in Patients With Severe Rheumatic Heart Disease: A Presidential Advisory From the American Heart Association. J Am Heart Assoc. 2022 Mar;11(5):e024517.

47. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004 Nov;39(9):1267-84.

48. Siqueira-Batista R, Gomes AP. Antimicrobianos: guia prático. 3rd ed. Rio de Janeiro (RJ): Rubio; 2021.

49. Barlow GD, Nathwani D. Sequential antibiotic therapy. Curr Opin Infect Dis. 2000;13(6):599-607.

50. Béïque L, Zvonar R. Addressing concerns about changing the route of antimicrobial administration from intravenous to oral in adult inpatients. Can J Hosp Pharm. 2015 Jul/Aug;68(4):318-26.

51. Carcione D, Siracusa C, Sulejmani A, Leoni V, Intra J. Old and new beta-lactamase inhibitors: molecular structure, mechanism of action, and clinical use. Antibiotics. 2021;10(8):995.

52. Gaber CE, Kinlaw AC, Edwards JK, Lund JL, Stürmer T, Hinton SP, et al. Comparative effectiveness and harms of antibiotics for outpatient diverticulitis. Ann Intern Med. 2021 Jun;174(6):737-46.

53. Levin AS, Levy CE, Manrique AEI, Medeiros EAS, Costa SF. Severe nosocomial infections with imipenem-resistant Acinetobacter baumannii treated with ampicillin/sulbactam. Int J Antimicrob Agents. 2003;21(1):58-62.

54. Betrosian AP, Frantzeskaki F, Xanthaki A, Georgiadis G. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant Acinetobacter baumannii. Scand J Infect Dis. 2007;39(1):38-43.

55. Lin HS, Lee MH, Cheng CW, Hsu PC, Leu HS, Huang CT, et al. Sulbactam treatment for pneumonia involving multidrug-resistant Acinetobacter calcoaceticus-Acinetobacter baumannii complex. Infect Dis (Lond). 2015 Jun;47(6):370-8.

56. Oliveira MS. Tratamento de infecções causadas por Acinetobacter spp. resistente a carbapenem [dissertação]. São Paulo: Universidade de São Paulo (USP) - Faculdade de Medicina; 2008.

57. Chagas TPG. Caracterização de Acinetobacter spp. multirresistentes produtores de carbapenemases, dos tipos OXA e NDM, isolados de diferentes regiões do Brasil. Rio de Janeiro [tese]. São Paulo: Instituto Oswaldo Cruz, Fundação Oswaldo Cruz; 2015.

58. Machado OVO, Patrocínio MCA, Medeiros MS, Bandeira TJPG. Antimicrobianos: revisão geral para graduandos e generalistas. Fortaleza: EdUnichristus; 2019.

59. Sittner A, Ben-Shmuel A, Glinert I, Bar-David E, Schlomovitz J, Kobiler D, et al. Using old antibiotics to treat ancient bacterium-β-lactams for Bacillus anthracis meningitis. PLoS One. 2020 Feb;15(2):e0228917.

60. Greene SE, Fritz SA. Infectious complications of bite injuries. Infect Dis Clin North Am. 2021;35(1):219-36.

61. McDanel JS, Perencevich EN, Diekema DJ, Herwaldt LA, Smith TC, Chrischilles EA, et al. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible staphylococcus aureus bloodstream infections among 122 hospitals. Clin Infect Dis. 2015 Aug;61(3):361-7.

62. Ministry of Health (BR). Relação Nacional de Medicamentos Essenciais: Rename 2020. Brasília (DF): Ministry of Health; 2020.

63. Tamma PD, Rodriguez-Baño J. The Use of noncarbapenem β-lactams for the treatment of extended-spectrum β-lactamase infections. Clin Infect Dis. 2017;64(7):972-80.

64. Sharara SL, Amoah J, Pana ZD, Simner PJ, Cosgrove SE, Tamma PD. Is piperacillin-tazobactam effective for the treatment of pyelonephritis caused by extended-spectrum β-lactamase-producing organisms? Clin Infect Dis. 2020;71(8):e331-e7.

65. Adler A, Katz DE, Marchaim D. The continuing plague of extended-spectrum β-lactamase producing enterbacterales infections. Infect Dis Clin North Am. 2020;34(4):677-708.

66. Rhodes NJ, Liu J, O'Donnell JN, Dulhunty JM, Abdul-Aziz MH, Berko PY, et al. Prolonged infusion piperacillin-tazobactam decreases mortality and improves outcomes in severely ill patients. Crit Care Med. 2018 Feb;46(2):236-43.

67. Yang H, Cui X, Ma Z, Liu L. Evaluation outcomes associated with alternative dosing strategies for piperacillin/tazobactam: a systematic review and meta-analysis. J Pharm Pharm Sci. 2016;19(2):274-89.

68. Wolf MF, Simon A. The use of piperacillin-tazobactam in neonatal and paediatric patients. Expert Opin Drug Metab Toxicol. 2009 Jan;5(1):57-69.

69. Bellos I, Karageorgiou V, Pergialiotis V, Perrea DN. Acute kidney injury following the concurrent administration of antipseudomonal β-lactams and vancomycin: a network meta-analysis. Clin Microbiol Infect. 2020;26(6):696-705.

70. Serna C, Gonzalez-Zorn B. Antimicrobial resistance and One Health. Rev Esp Quimioter. 2022;35(Suppl 3):S37-S40.

71. Velazquez-Meza ME, Galarde-López M, Carrillo-Quiróz B, Alpuche-Aranda CM. Antimicrobial resistance: One Health approach. Vet World. 2022;15(3):743-9.

72. Diallo OO, Baron SA, Abat C, Colson P, Chaudet H, Rolain JM. Antibiotic resistance surveillance systems: a review. J Glob Antimicrob Resist. 2020 Dec;23:430-8.

73. Alves MMR, Lara MAG, Gomes AP, Gazineo JLD, Braga LM, Castro ASB, Siqueira-Batista R. Penicilina G: atualização. Rev Saúde Dinâmica 2022;12:66-89.

74. Schechter M. Antibióticos: uso clínico. In: Schechter M, Marangoni D, eds. Doenças infecciosas: conduta diagnóstica e terapêutica. 2nd ed. São Paulo: Guanabara Koogan; 1998.

75. Osler W. On the educational value of the medical society. Bost Med Surg J. 1903;148(11):275-9.