AMINOGLYCOSIDES IN THE 21ST CENTURY: REVIEW AND UPDATE, WITH EMPHASIS ON NEPHROTOXICITY

Jorge Luiz Dutra Gazineo, Guilherme Fiorino Bissoli, Gustavo Canaan Barros Lima, Ramon Aragão Dutra Neto, Ranielle Bruno dos Santos, Renato Ismael Cordeiro de Souza, Andréia Patrícia Gomes, Adriano Simões Barbosa Castro, Luiz Alberto Santana e Rodrigo Siqueira Batista. *Aminoglycosides in the 21st century: review and update, with emphasis on nephrotoxicity. Revista Saúde Dinâmica, vol. 5, núm.2, 2023. Faculdade Dinâmica do Vale do Piranga.*

SAÚDE DINÂMICA – Revista Científica Eletrônica
FACULDADE DINÂMICA DO VALE DO PIRANGA

14ªth Edition 2023 | Year VI – nº 2 | ISSN – 2675-133X

DOI:10.4322/2675-133X.2023.010

2º semestre de 2023

FACULDADE Dinâmica FORMANDO PESSOAS

Aminoglycosides in the 21st century: Review and update, with emphasis on nephrotoxicity

Aminoglicosídeos no Século 21: Revisão e atualização, com ênfase na nefrotoxicidade

Jorge Luiz Dutra Gazineo[1], Guilherme Fiorino Bissoli[2], Gustavo Canaan Barros Lima[3], Ramon Aragão Dutra Neto[4], Ranielle Bruno dos Santos[5], Renato Ismael Cordeiro de Souza[6], Andréia Patrícia Gomes[7], Adriano Simões Barbosa Castro[8], Luiz Alberto Santana[9] e Rodrigo Siqueira Batista[10].

[1]Médico do Serviço de Doenças Infecciosas e Parasitárias, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brasil. ORCID: 0000-0001-5430-1181

[2]Discente do Curso de Medicina, Faculdade Dinâmica do Vale do Piranga,ORCID: 0000-0001-6374-6043.

[3]Discente do Curso de Medicina, Faculdade Dinâmica do Vale do Piranga, ORCID: 0000-0002-4880-5321.

[4]Discente do Curso de Medicina, Faculdade Dinâmica do Vale do Piranga, ORCID: 0000-0003-0385-7678.

[5]Discente do Curso de Medicina, Faculdade Dinâmica do Vale do Piranga, ORCID: 0000-0002-9564-0208.

[6]Discente do Curso de Medicina, Faculdade Dinâmica do Vale do Piranga, ORCID: 0000-0002-6327-5410.

[7]Professora Associada do Departamento de Medicina e Enfermagem, Universidade Federal de Viçosa, Viçosa, MG, Brasil. ORCID: 0000-0002-5046-6883

[8]Professor Adjunto da Escola de Medicina, Faculdade Dinâmica do Vale do Piranga, ORCID: 0000-0003-3175-0341.

[9]Professor Associado do Departamento de Medicina e Enfermagem, Universidade Federal de Viçosa, Viçosa, MG, Brasil. ORCID: 0000-0002-6436-7958

[10] Professor Titular da Escola de Medicina, Faculdade Dinâmica do Vale do Piranga, Ponte Nova, MG, Brasil. Professor Titular do Departamento de Medicina e Enfermagem, Universidade Federal de Viçosa, Viçosa, Minas Gerais, Brasil. ORCID: 0000-0002-3661-1570.

Autor correspondente: rsbatista@ufv.br

ABSTRACT: Introduction: Aminoglycosides are bactericidal antimicrobials that show great activity against aerobic gram-negative bacteria, which makes them important allies in the treatment of different infectious conditions. However, their use deserves special care in relation to potential adverse effects, particularly those related to renal alterations. **Objective**: To review the current use of aminoglycosides, highlighting their clinical applicability and nephrotoxicity. **Methods**: Bibliographical research of the narrative review type. **Results and Discussion**: The main characteristics of the drugs were described in the section "*General aspects of aminoglycosides*". This section contains comments on the chemical structure, mechanism of action, antimicrobial resistance and clinical use of aminoglycosides, with an emphasis on a new drug, plazomicin. The adverse effects on the kidneys are highlighted in the section "*Nephrotoxicity of aminoglycosides*", with emphasis on the main risk factors related to their occurrence. **Conclusion**: Aminoglycosides remain drugs of significant importance in the treatment of bacterial infections, due to their efficacy and low cost; nephrotoxicity is a possible consequence of the use of these drugs, so strategies to reduce it should be undertaken and better investigated.

Keywords: Aminoglycosides, Anti-Infective Agents, Acute Kidney Injury.

RESUMO: Introdução: Os aminoglicosídeos são antimicrobianos bactericidas que apresentam grande atividade contra bactérias gram-negativas aeróbias, o que os torna importantes aliados no tratamento de diferentes condições infecciosas. Todavia, seu uso merece cuidado especial em relação aos potenciais efeitos adversos, particularmente aqueles relativos às alterações renais. **Objetivo**: Revisar o uso dos aminoglicosídeos na atualidade, com destaque para sua aplicabilidade clínica e para sua nefrotoxicidade. **Métodos**: pesquisa bibliográfica do tipo revisão narrativa. **Resultados e Discussão**: As principais características dos fármacos foram descritas na seção "*Aspectos gerais dos aminoglicosídeos*". Nesta constam comentários sobre a estrutura química, o mecanismo de ação, a resistência antimicrobiana e o uso clínico dos aminoglicosídeos, com ênfase em um novo medicamento, a plazomicina. Os efeitos adversos em nível renal são ressaltados na seção "*Nefrotoxicidade dos aminoglicosídeos*", com destaque para os principais fatores de risco relacionado à sua ocorrência. **Conclusão**: Os aminoglicosídeos permanecem como fármacos de significativa importância no tratamento de infecções bacterianas, devido à sua eficácia e ao seu baixo custo; a nefrotoxicidade é uma consequência possível do uso desses medicamentos, de modo que as estratégias para minorá-la devem ser empreendidas e melhor investigadas.

Palavras-Chave: Aminoglicosídeos, Anti-Infecciosos, Injúria Renal Aguda.

INTRODUCTION

Aminoglycosides are bactericidal antimicrobials made up of two or more amino sugars joined to an aminocyclitol ring by glycosidic bonds, which means that they contain a large number of NH_2 and OH radicals and are therefore polycationic in nature. These drugs show great activity against aerobic gram-negative bacteria and limited *in vitro* activity against gram-positive bacteria. In fact, their use in infections caused by the latter should be associated with the concomitant use of beta-lactam antibiotics, in order to achieve a synergistic effect in treatment (JACKSON et al., 2013; SIQUEIRA-BATISTA and GOMES, 2021). All *Streptococcus* – including *Streptococcus pneumoniae* – are resistant to aminoglycosides (LEGGET, 2020). In addition, they have no activity against strict anaerobic bacteria, *Burkholderia cepacia, Stenotrophomonas maltophilia* and *Pasturella multocida* (JACKSON, et al., 2013). Meanwhile, aminoglycosides are very important drugs in the treatment of infectious conditions, mainly of the urinary tract, including

hospital-acquired infections caused by gram-negative bacilli that are multidrug-resistant (AMINOGLYCOSIDES, 2019; AMINOGLYCOSIDES, 2022; ANVISA, 2022).

In terms of their mechanism of action, aminoglycosides, by binding to the 30S fraction of ribosomes, inhibit protein synthesis or cause the production of defective proteins. In order to act, these drugs have to bind to the surface of the bacterial cell, for subsequent transportation through the cell wall by an active mechanism, aided by the transmembrane electrical potential (positive charge of the antimicrobial and negative charge of the intracellular medium) of the bacteria. However, taking into account the polycationic nature and polar characteristics of aminoglycosides, these drugs find it difficult to cross lipid bacterial membranes, particularly those of gram-negative bacteria, as they are insoluble in organic solvents (LEGGET, 2020).

Unlike beta-lactams and quinolones, aminoglycosides have considerable intrinsic toxicity, including nephrotoxicity (damage to the proximal renal convoluted tubules) and ototoxicity (damage to the cochlea and vestibular apparatus), which can occur in 2 to 15% of patients. In addition, the focus of infection (central nervous system or prostate), the local pH (acidic pH of bronchial secretions) and the presence of tissue necrosis and hypoxemia (abscesses) also affect their antimicrobial activity. Another limitation of the use of these antibiotics is the need for frequent monitoring of their serum levels to avoid underdoses or toxicities (REESE, BETTS 2003).

Based on these preliminary considerations, this article aims to (1) review the use of aminoglycosides – with an emphasis on the nephrotoxicity that can be associated with their use – and (2) update knowledge on the subject by presenting a new antibiotic in this class, plazomicin, which should be available for clinical use in the next few years in Brazil.

METHODS

This research was based on a bibliographic search to create a narrative literature review, a type of study which scope is to describe and discuss the "*state of science of a specific theme or topic from a theoretical and contextual point of view*" (BOTELHO, 2011, p. 125). This research technique deserves to be highlighted insofar as it represents "*a non-systematized way of reviewing the literature*" with the aim of "*seeking updates on a particular subject*" (CASARIN et al., 2020,

p. 1). In fact, it is applicable to the assessment of a broader research problem, with the aim of delimiting its state of the art. To this end, a "*critical analysis of the literature published in books and electronic or paper-based journal articles*" (ROTHER, 2007, p. vii) was carried out, based on a non-systematic search, with a focus on gathering scientific evidence to update the main aspects of aminoglycosides, with an emphasis on the nephrotoxicity of these drugs.

At the end of the process of free – non-systematic – selection and reading of the articles, 50 texts were chosen to make up this review. The results, as shown below, have been organized into two sections: (1) "General aspects of aminoglycosides" and (2) "Nephrotoxicity of aminoglycosides".

RESULTS AND DISCUSSION

GENERAL ASPECTS OF AMINOGLYCOSIDES

Historical note

Aminoglycosides were synthesized from the fungus *Streptomyces griseus* in the 1940s (TAVARES, 2020). The drug initially obtained for use in clinical practice was streptomycin, which became the first active antimicrobial in the treatment of tuberculosis. The discovery and effectiveness of streptomycin's antibacterial activity earned Selman Waksman and collaborators a nomination for the Nobel Prize in Medicine (TAVARES, 2020).

Classification of aminoglycosides

Currently, aminoglycosides can be classified, in terms of their production, into natural and semi-synthetic. The former include the aforementioned streptomycin; the semi-synthetic amikacin stands out, used mainly to treat infections caused by aerobic gram-negative bacteria, with a better toxicity profile (TAVARES, 2020; BRUNTON et al., 2018).

Chemical structure of aminoglycosides

These antimicrobials are hydrophilic and have amino sugars linked to an aminocyclitol ring derived from inositol by glycosidic bonds. They also have NH_2 and OH bonds, respectively, to acetylase and adenylase, as they are polycationic in nature. They are very active *in vitro* against

aerobic gram-negative bacteria (BRUNTON et al., 2018). Aerobic gram-positive bacteria, on the other hand, are relatively resistant to aminoglycosides (JACKSON et al., 2013). The drugs have a molecular weight of between 445 and 600 daltons, are highly soluble in water, stable at pH 6 to 8 and have a polar cationic structure (AMINOGLYCOSIDES, 2019; AMINOGLYCOSIDES, 2022; BRUNTON et al., 2018). The drugs are not affected by the effect of the bacterial inoculum and all exhibit a post-antibiotic effect (LEGGET, 2020).

Mechanism of action

The mechanism of action of aminoglycosides differs from that of other antibiotics. In fact, they bind to the 30s ribosomal subunit and cause incorrect reading of the ribosome's genetic code, inhibiting protein synthesis and leading to the formation of aberrant proteins. In addition, they cause electrostatic changes in the bacterial plasma membrane – because they are cationic drugs, causing changes in cell permeability – breaking its osmotic protection, which can lead to cell death (AMINOGLYCOSIDES, 2019; AMINOGLYCOSIDES, 2022; BRUNTON et al., 2018; TAVARES, 2020). Thus, there is a mixed action: inhibition of ribosomal activity, with dysfunctions in protein synthesis, formation of defective peptides and modifications to the plasma membrane. In fact, the final combined action of aminoglycosides is bactericidal, with a mechanism of action that is distinct from other classes of antibiotics.

Microbial resistance

The frequency of resistance to aminoglycosides remains low and the emergence of bacterial resistance during therapy has been rare (LEGGET, 2020). Bacterial resistance to aminoglycosides is mainly due to the action of drug-modifying enzymes, hyper-expression of efflux pump activity and methylation of the 16s rRNA ribosomal subunit, leading to structural modification of antibiotics and a decrease in their concentration within bacteria (TEVYASHOVA, SHAPOVALOVA, 2021; WANG et al., 2022). Intrinsic resistance to aminoglycosides can be caused by changes in the permeability of the outer membrane, or by a defect in transporting the drug into the cell. The drugs also induce bacterial biofilm formation, with adhesion to the surface of the bacterial cell wall (LEGGET, 2020).

The most common resistance refers to the acquisition of plasmids or genes that encode transposons for enzymes that modify aminoglycosides (acetyltransferases, adenyltransferases and phosphotransferases). Subsequently, cross-resistance can occur between drugs of the same class. The genes that code for aminoglycoside-modifying enzymes are acquired primarily by association and plasmid transfer (LEGGET, 2020). Amikacin is a good substrate for only some of these inactivating enzymes, so strains that are resistant to other aminoglycosides tend to be susceptible to amikacin. It is worth noting that resistance to gentamicin leads to cross-resistance with tobramycin, amikacin, kanamycin and netilmicin (LEGGET, 2020).

Resistance to aminoglycosides in bacteria of the genus *Enterococcus* commonly comes from the acquisition of plasmid-borne aminoglycoside-modifying enzymes. *Enterococcus faecalis* strains with high-level resistance to gentamicin, defined as a minimum inhibitory concentration (MIC) > 2000 µg/ml, are resistant to most other aminoglycosides, although some of them are susceptible to streptomycin (BADDOUR et al., 2015).

Streptomycin

Streptomycin – the first antibiotic in its class to be commercially launched in 1944 – has an aminocyclitol ring which is called streptidine, unlike the other aminoglycosides (LEGGET, 2020). It is used in the treatment of multidrug-resistant (MDR) tuberculosis or in chronic liver disease or in patients who have experienced hepatoxicity with the preferred tuberculosis treatment regimen (rifampicin, isoniazid, pyrazinamide and ethambutol). The use of streptomycin in such therapeutic regimens (maximum dose of one gram/day) is conditional on the patient not having used it before and on a sensitivity test (ST) showing sensitivity. In the absence of a TS, streptomycin should not be used (AMINOGLYCOSIDES, 2019; AMINOGLYCOSIDES, 2022; BRASIL, 2019). In addition to tuberculosis, other clinical indications for streptomycin are: treatment of plague and tularemia (JACKSON, 2013; REESE, 2003; SANTANA et al., 2016).

Capreomycin

In the treatment of MDR tuberculosis, capreomycin is the preferred aminoglycoside due to its better tolerance, lower likelihood of adverse reactions and lower possibility of cross-resistance with amikacin, preserving its use for future alternative regimens in the event of

therapeutic failure or extensively resistant tuberculosis (XDR). When capreomycin cannot be used, its substitute should be amikacin (AMINOGLYCOSIDES, 2019; AMINOGLYCOSIDES, 2022; BRASIL, 2019).

Neomycin, paramomycin and spectinomycin

Neomycin is used orally to treat hepatic encephalopathy. Because it is poorly absorbed orally, neomycin causes a decrease in intestinal bacterial populations, thus reducing the production and absorption of ammonia in the colon. Paromomycin is a non-absorbable aminoglycoside that concentrates in the colon lumen and has activity against some *protozoa* (*Entamoeba histolytica*, *Dientamoeba fragilis*, *Giardia lamblia* and *Leishmania* spp.) and cestodes (*Taenia saginata*, *Taenia solium*, *Diphyllobothrium latum*, *Dipylidium caninum* and *Hymenolepis nana*) (TAVARES, 2020; BRUNTON et al., 2018). Spectinomycin is an aminocyclitol antibiotic (chemical structure similar to that of aminoglycosides) used as an alternative treatment for gonococcal infections (except for pharyngeal involvement), and is indicated for those allergic to beta-lactams or those infected with resistant strains of *Neisseria gonorrhoeae* (LEGGET, 2020; REESE, BETTS 2003; DAVIDSON et al., 2009).

Tobramycin and amikacin

Tobramycin, at a starting dose of 7mg/kg/day (with adjusted body weight in obese patients) and amikacin, at a starting dose of 20mg/kg/day (with adjusted body weight in obese patients), are administered parenterally (LEGGET, 2020). They are used to treat serious infections, usually associated with penicillins or cephalosporins (ALVES et al., 2022; SIQUEIRA-BATISTA et al., 2023; TAVARES, 2020). Amikacin has *in vitro* activity against severe and cavitary forms of the CMA group (*Mycobacterium avium, M. intracellulare, M. chimaera, M. colombiense, M. arosiense, M. vulneris, M. bouchedurhonense,* M. *timonense, M. marseillense, M. yongonense, M.* paraintracellulare *and M. lepraemurium*), the M. *abscessus* group (*M. abscessus abscessus, M. abscessus* massiliense *and M. abscessus bolletii*), the *M. fortuitum complex* (M. *fortuitum, M. peregrinum, M. senegalense, M. porcinum, M. neworleansense, M.boenickei, M. houstonense, M. brisbanense, M. septicum,* and *M. setense),* M. *chelonae* group (*M. chelonae chelonae, M. chelonae bovis* and *M. chelonae gwanakae),* severe and cavitary forms of M. *kansasii* and *M. tuberculosis* MDR (AMINOGLYCOSIDES, 2019; AMINOGLYCOSIDES, 2022; BRASIL, 2021; BRASIL, 2019; TAVARES, 2020). In addition,

amikacin has *in vitro* activity against *Nocardia* spp. Tobramycin can be administered via nebulization in the maintenance treatment of cystic fibrosis or tracheobronchitis caused by *Pseudomonas aeruginosa* (LEGGET, 2020).

Gentamicin

Gentamicin, at a starting dose of 7 mg/kg/day (body weight adjusted in obese patients), is recommended for the treatment of many serious infections caused by aerobic gram-negative bacilli (HODIAMONT et al., 2022). In general, this drug is preferred because of its low cost and its reliable activity against all aerobic gram-negative bacilli. Gentamicin formulations are available for parenteral (intravenous and intramuscular), ophthalmic and topical administration. Variations in the composition of commercial gentamicin formulations associated with differences in toxicity between gentamicin congeners suggest that some gentamicin formulations may be more nephrotoxic (BULMAN et al., 2020).

Plazomicin

In 2018, plazomicin was authorized for clinical use by the *Food and Drug Administration* (FDA), with intravenous (IV) administration, at a starting dose of 15mg/kg/day (with adjusted body weibght in obese patients), as monotherapy for complicated urinary tract infections and acute pyelonephritis, caused by enterobacteria, including MDR strains (CLANCY, NGUYEN, 2022; CLARK, BURGESS 2020; WAGENLEHNER et al., 2019). For the treatment of cystitis caused by enterobacteriaceae and *P. aeruginosa* (including MDR strains), a single dose of 15mg/kg (body weight adjusted in obese patients) IV, is recommended (CLANCY, NGUYEN, 2022; TAMMA et al., 2022). A recent meta-analysis of randomized clinical trials showed that plazomicin would be a suitable choice for the treatment of adults with complicated urinary tract infections, bloodstream infections or healthcare-related pneumonia (YAN, 2022).

Plazomicin is a semi-synthetic aminoglycoside that has been structurally modified to avoid inactivation by most aminoglycoside-modifying enzymes and is active *in vitro* against most enterobacteria, including those producing extended-spectrum beta-lactamases (ESBLs), class C ampicillinases (AmpC) and most carbapenem-resistant enterobacteriaceae (ERCs), except those producing the metallo-beta-lactamase NDM-1 (BASSETTI et al., 2021; CLANCY, NGUYEN, 2022; DOI, 2019; TOMPKINS, VAN DUIN, 2021). Plazomicin resistance is most commonly caused by the production of 16S ribosomal RNA methylases, including ArmA, RmtA, RmtB and

RmtC, which inactivate all aminoglycosides (BUSH, 2017). The drug is also highly active against *Staphylococcus aureus* and coagulase-negative *Staphylococcus*, including methicillin-resistant strains. However, it has no predictable *in vitro* activity against *Acinetobacter* spp. (BASSETTI et al., 2021; DOI, 2019; TOMPKINS, VAN DUIN, 2021).

Use of aminoglycosides combined with other antimicrobials

In combination with an antimicrobial that acts on the cell wall, such as penicillin or ampicillin, aminoglycoside exerts a bactericidal action on infective endocarditis (IE) caused by *Enterocccus* spp. (without high-level resistance to aminoglycosides), *Streptococcus viridans* and *Streptococcus gallolyticus* with a MIC to penicillin ≥ 0.5µg/ml, *Abiotrophia defectiva* and *Granulicatella spp*. (CHAMBERS, BAYER, 2020). However, in a scenario of progressively increasing age and frailty of patients with IE, the time of use of aminoglycosides can be reduced (two weeks) or avoided in approximately 90% of cases. This should lead to a reduction in the incidence of renal failure, an important prognostic factor in IE (LEBEAUX et al., 2020).

Results of meta-analysis showed that combined treatment with aminoglycosides increased nephrotoxicity without improving efficacy in neutropenic patients with bacteremia (PAUL et al., 2004; PAUL et al., 2014), However, recent retrospective studies have concluded that the combination therapy of beta-lactams with aminoglycosides (including a single dose of gentamicin), administered promptly in the treatment of patients with sepsis or septic shock (including *P. aeruginosa* bacteremia), is associated with lower mortality compared to monotherapy with beta-lactams. Based on the results of these studies, antibiotic therapy combined with an aminoglycoside could be considered in neutropenic patients with shock. However, controlled clinical trials are needed to confirm the results of these studies (ALBASANZ-PUIG et al., 2022; CHUMBITA et al., 2022; LILJEDAHL et al., 2020).

Adverse events of aminoglycosides

Aminoglycoside-induced ototoxicity has been reported in 2 to 45% of adults. Ototoxicity can be vestibular and/or cochlear and is typically dose-dependent. This side effect can appear during or after treatment. Gentamicin, streptomycin and tobramycin most often cause vestibular lesions, while amikacin and kanamycin (discontinued use in the USA) cause more cochlear

lesions. Studies have revealed that aminoglycosides appear to generate oxygen compounds in the inner ear that cause damage to vestibular and cochlear sensory cells, as well as cochlear neurons. Vestibular loss can often be recovered, while high-frequency hearing loss is usually irreversible (BLOCK, BLANCHARD, 2022; REESE, BETTS 2003).

Neuromuscular blockade is an uncommon and toxic reaction that has been described as a side effect of using aminoglycosides. It is seen in special situations, such as the absorption of high doses administered via the peritoneal route (no longer used today) or due to rapid infusions of the drug. Some patients are more susceptible to this complication, such as those with myasthenia gravis, hyperphosphatemia, hypercalcemia and botulism, situations in which the concomitant use of aminoglycosides should be indicated exceptionally (REESE, BETTS 2003).

Other (rare) adverse effects include hypersensitivity – for example, skin rashes, eosinophilia, angioedema, exfoliative dermatitis, stomatitis and anaphylactic shock – as well as fever and blood dyscrasias (REESE, BETTS 2003).

Nephrotoxicity is one of the most significant adverse effects of aminoglycosides (SIQUEIRA-BATISTA, GOMES 2021), so this occurrence will be detailed in the next section.

NEPHROTOXICITY OF AMINOGLYCOSIDES

Nephrotoxicity, although less frequent than hearing damage, is particularly important as it can cause a progressive accumulation of aminoglycosides and, consequently, an increase in all their toxic effects (HUMES, 1988; LE et al., 2023). It is one of the most important adverse events linked to exposure to these drugs, related to a variable degree of renal tubular dysfunction, which can lead to non-oliguric acute kidney injury (AKI) in the most severely affected patients. Between 8 and 26% of patients who are continuously administered aminoglycosides develop mild renal impairment, which in most cases is reversible. Toxicity is caused by the accumulation and retention of the drug in the proximal tubular cells. The initial manifestation of damage at this site consists of the elimination of enzymes from the renal tubular cells, followed by mild proteinuria. The percentage of glomerular filtration decreases over the days (HUMES, 1988; LE et al., 2023; LOPEZ-NOVOA et al., 2011; NAGAI, TAKANO, 2004).

All aminoglycosides are potentially nephrotoxic. Nephrotoxicity usually appears seven to ten days after the start of treatment and is characterized as acute renal failure (ARF) of the non-

oliguric type. oliguric type, acute tubular necrosis, proteinuria, enzymuria, aminoaciduria, glycosuria and electrolyte alterations (hypercalciuria, hypermagnesuria, hypocalcemia and hypomagnesemia) may occur. This complication can be reversible with the cessation of treatment (DOBREK, 2023; LOPEZ-NOVOA et al., 2011; SCHECHTER, 1998).

Likewise, it is recognized that among the aminoglycosides used parenterally, the least nephrotoxic is streptomycin, and the toxicity of the other drugs is very similar, although it is recognized that neomycin is extremely nephrotoxic (BRUNTON et al., 2018). On the other hand, studies suggest that tobramycin is less nephrotoxic than amikacin, kanamycin or netilmicin, while gentamicin is considered to be more nephrotoxic than the latter (HUMES, 1988).

Nephrotoxicity is a very common feature of aminoglycosides, with an incidence ranging from 5 to 25%. Once a patient has ARF secondary to the use of an aminoglycoside, their renal function may not return to baseline (CLIFFORD et al., 2022).

There are various risk factors for nephrotoxicity which may be related to (1) the patient, (2) aminoglycosides or (3) the use of other compounds (drug interactions). With regard to the patient, these include advanced age, diabetes mellitus, previous kidney disease, male gender, systemic arterial hypotension, liver dysfunction, hypoalbuminemia (<3.0 g/dl) and anemia (hemoglobin levels <11.6 g/dl) (CLIFFORD et al., 2022; CHOU et al., 2022). With regard to aminoglycosides, the use of the drug for more than 72 hours, multiple doses administered daily, cumulative doses, high serum levels and recent use (CLIFFORD et al., 2022). Some associated drugs can cause nephrotoxicity to worsen, including: vancomycin, furosemide, cephalosporins (especially first-generation cephalosporins), iodinated radiological contrast, foscarnet, cidofovir, amphotericin B, non-hormonal anti-inflammatory drugs and cyclosporine (LOPES-NOVOA et al., 2011).

Nephrotoxicity is related to the drug's binding to the proximal tubule. There are specific receptors in the tubule where endocytosis of the aminoglycoside occurs. The tubular membrane is home to megalin, which is an endocytic receptor responsible for the reabsorption of glomerular filtrate. Megalin is associated with the formation of myeloid bodies, and with this, there is an accumulation of aminoglycosides in the proximal tubular cells (around 10% of the dose), where they can induce apoptosis and acute tubular necrosis, due to the interruption of phospholipid metabolism (HUMES, 1988; NAGAI, TAKANO, 2004). These abnormalities can lead to

significant tubular obstruction. However, reduced glomerular filtration is necessary to explain the manifestations of this morbid condition. Reduced filtration is not only the result of tubular obstruction and tubular malfunction; renal vasoconstriction and mesangial contraction are also crucial to comprehensively explain the nephrotoxicity of aminoglycosides (DOBREK, 2023; LOPES-NOVOA et al., 2011).

Prolonged treatment with aminoglycosides (for more than seven days) can lead to ARF and a drop in glomerular filtration. In this case, nephrotoxicity is manifested by an increase in serum creatinine. Therefore, this nitrogenous slag should be measured every 2-4 days in patients taking aminoglycosides (REESE, BETTS, 2003). In most cases, renal function is recovered and treatment is supportive (e.g. correction of hypovolemia), considering the suspension and replacement of the aminoglycoside with another antimicrobial. Recently, an experimental study revealed that mannitol can directly protect human kidney cells from the cytotoxicity of aminoglycosides, reducing the effective concentrations of these antibiotics, regardless of the effect of the metabolite on the bacteria (ROSENBERG et al., 2020). It is also worth mentioning that penicillins with *anti-Pseudomonas* activity – carbenicillin and ticarcillin (SIQUEIRA-BATISTA et al., 2023) –, when administered concomitantly with aminoglycosides in febrile neutropenic patients, have been shown to be useful in reducing their nephrotoxic effect (LEGGET, 2020). Frequent monitoring of serum levels (at peak and trough times) and the use of single daily doses for a short period of time (ideally less than seven days) also help to minimize the risk of ARF in patients requiring an aminoglycoside prescription (BÖTTGER, CRICH, 2020; CLIFFORD et al., 2022; DRUSANO, LOUIE, 2011; HODIAMONT et al., 2022; HUMES, 1988). Indeed, perhaps the most promising way of preventing aminoglycoside-induced nephrotoxicity is by inhibiting their uptake in the proximal tubules with the use of effective and safe megalin antagonists (NAGAI, TAKANO, 2004).

FINAL CONSIDERATIONS

This article was written with the aim of reviewing the main aspects of aminoglycosides – with an approach to the new perspectives for their use, particularly in relation to plazomicin –

and updating the knowledge regarding nephrotoxicity, explaining its mechanisms and correlated factors.

It is hoped that the concepts presented here can be useful for the correct – and safe – prescription of this class of drugs, helping to maximize therapeutic indications and reduce adverse effects, factors that combined can contribute to the care of victims of infectious processes, especially those caused by aerobic gram-negative bacteria.

REFERENCES

ALBASANZ-PUIG, A.; DURÀ-MIRALLES X.; LAPORTE-AMARGÓ, J.; MUSSETT A.; RUIZ-CAMPS I.; PUERTA-ALCALDE P.; ABDALA E.; OLTOLINI, C. AKOVA M. MONTEJO, J.M.; MIKULSKA, M.; MARTÍN-DÁVILA, P.; HERRERA, F.; GASCH, O.; DRGONA, L.; MORALES, H. M. P.; BRUNEL, A. S.; GARCÍA, E.; ISLER, B.; KERN, W. V.; RETAMAR-GENTIL, P.; AGUADO, J. M.; MONTERO, M.; KANJ, S. S.; SIPAHI, O. R.; CALIK, S.; MÁRQUEZ-GÓMEZ, I.; MARIN, J. I.; GOMES, M. Z. R.; HEMMATI, P.; ARAOS, R.; PEGHIN, M.; POZO, J. L.; YÁÑEZ, L.; TILLEY, R.; MANZUR, A.; NOVO, A.; PALLARÈS, N.; BERGAS, A.; CARRATALÀ, J.; GUDIOL, C. Effect of combination antibiotic empirical therapy on mortality in neutropenic cancer patients with *Pseudomonas aeruginosa* pneumonia. **Microorganisms**, v. 10, p. 733, 2022. Disponível em: https://doi.org/10.3390/ microorganisms10040733. Acesso em: 31 jul. 2023.

ALVES, M. M. R.; LARA, M. A. G.; GOMES, A. P.; GAZINEO, J. L. D.; BRAGA, L. M.; CASTRO, A. S. B.; SIQUEIRA-BATISTA, R. Penicilina G: atualização. **Revista Saúde Dinâmica**, v. 12, p. 66-89, 2022. Disponível em: http://revista.faculdadedinamica.com.br/index.php/saudedinamica/article/view/137. Acesso em: 15 mai. 2022.

AMINOGLICOSIDEOS. Disponível em: https://www.anvisa.gov.br/servicosaude/controle/rede_rm/cursos/rm_controle/opas_web/modulo1/aminoglicosideos6.htm. Acesso em: 15 out. 2022.

AMINOGLYCOSIDES. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK548232/. Acesso em: 15 out. 2022.

ANVISA. **Antimicrobianos: bases teóricas e uso clínico**. Anvisa, 2007. Disponível em: https://www.anvisa.gov.br/servicosaude/controle/rede_rm/cursos/rm_controle/opas_web/modulo1/aminoglicosideos6.htm. Acesso em: 15 out 2022.

BADDOUR, L. M.; WILSON, W. R.; BAYER, A. S.; FOWLER Jr., V. G.; TLEYJEH, I. M.; et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. **Circulation**, v. 132, p. 1435-1486. Disponível em: 10.1161/CIR.0000000000000296. Acesso em: 31 jul. 2023.

BASSETTI, M.; GIACOBBE, D. R.; CASTALDO, N.; RUSSO, A.; VENA, A. Role of new antibiotics in extended-spectrum β-lactamase-, AmpC-infections. **Current Opinion in Infectious Diseases**, v. 34, n. 6, p. 748-755, 2021. Disponível em: 10.1097/QCO.0000000000000789. Acesso em: 30 set. 2023.

BLOCK, M.; BLANCHARD D. L. **Aminoglycosides**. Treasure Island (FL): StatPearls; 2022. Disponível em: http://www.ncb0i.nlm.nih.gov/books/NBK541105/. Acesso em: 21 out. 2023.

BOTELHO, L. L. R.; CUNHA, C. C. A.; MACEDO, M. O método da revisão integrativa nos estudos organizacionais. **Gestão e Sociedade**, v. 5, n. 11, p. 121, 2011. Disponível em: 10.21171/ges.v5i11.1220 19. Acesso em: 15 out. 2022.

BÖTTGER, E. C.; CRICH, D. Aminoglycosides: time for the resurrection of a neglected class of antibacterials? **ACS Infectious Diseases**, v. 6, n. 2, p. 168-172, 2020. Disponível em: 10.1021/acsinfecdis.9b00441. Acesso em: 21 out. 2023.

BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. **Recomendações para o diagnóstico e tratamento das doenças causadas por micobactérias não tuberculosas no Brasil**. Ministério da Saúde, Secretaria de Vigilância em Saúde, lDepartamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. Brasília: Ministério da Saúde, 2021. 93 p. Disponível em: http://antigo.aids.gov.br/pt-br/pub/2021/recomendacoes-para-o-diagnostico-e-tratamento-das-doencas-causadas-por-micobacterias-nao-0. Acesso em: 31 jul. 2022.

BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. **Manual de Recomendações para o Controle da Tuberculose no Brasil**. Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis. – Brasília: Ministério da Saúde, 2019. 364 p. Disponível em: http://antigo.aids.gov.br/pt-br/pub/2019/manual-de-recomendacoes-para-o-controle-da-tuberculose-no-brasil. Acesso em: 31 jul. 2022.

BRUNTON, L. L.; CHABNER, B. A.; KNOLLMANN, B. C. **As bases farmacológicas da terapêutica de Goodman e Gilman**. 13ª. ed. Porto Alegre: AMGH, 2018.

BULMAN, Z. P.; CIRZ, R.; HILDEBRANDT, D.; KANE, T.; ROSARIO, Z.; WLASICHUK, K.; PARK, M.; ANDREWS, L. D. Unraveling the gentamicin drug product complexity reveals variation in microbiological activities and nephrotoxicity. **Antimicrobial Agents and Chemotherapy**, v. 64, n. 9, p. e00533-20, 2020. Disponível em: 10.1128/AAC.00533-20. Acesso em: 15 out. 2022.

BUSH, K. Plazomicin. *In*: **Kucers' the use of antibiotics: a clinical review of antibacterial, antifungal, antiparasitic and antiviral drugs**. 7th ed. CRC Press, 2017, p. 1053-1062.

CASARIN, S. T.; PORTO, A. R.; GABATZ, R. I. B.; BONOW, C. A.; RIBEIRO, J. P.; MOTA, M. S. Tipos de revisão de literatura: considerações das editoras do Journal of Nursing and Health. **Journal of Nursing and Health**, v. 10, n. esp., p. e20104031, 2020. Disponível em:

https://periodicos.ufpel.edu.br/ojs2/index.php/enfermagem/article/view/19924. Acesso em: 01 set. 2023.

CHAMBERS, H. F.; BAYER, A. S. Native-valve infective endocarditis. **The New England Journal of Medicine**, v. 383, n. 6, p. 567-576, 2020. Disponível em: 10.1056/NEJMcp2000400. Acesso em: 15 out. 2022.

CHOU, C-L.; CHUANG, N-C.; CHIU, H-W.; LIAO, C-T.; HSU, Y-H.; CHANG, T-H. Aminoglycosides use has a risk of acute kidney injury in patients without prior chronic kidney disease. **Scientific Reports**, v. 12, p. 17212, 2022. Disponível em: 10.1038/s41598-022-21074-x. Acesso em: 30 set. 2023.

CHUMBITA, M.; PUERTA-ALCALDE, P.; GUDIOL, C.; GARCIA-POUTON, N.; LAPORTE-AMARGÓS, J. et al. Impact of empirical antibiotic regimens on mortality in neutropenic patients with bloodstream infection presenting with septic shock. **Antimicrobial Agents and Chemotherapy**, v. 66, n. 2, p. e01744-21, 2022. Disponível em: 10.1128/AAC.01744-21. Acesso em: 15 out. 2023.

CLANCY, C. J.; NGUYEN, M. H. Management of highly resistant gram-negative infections in the intensive care unit in the era of novel antibiotics. **Infectious Disease Clinics of North America**, v. 36, p. 791-823, 2022. Disponível em: https://doi.org/10.1016/j.idc.2022.08.004. Acesso em: 31 jul. 2023.

CLARK, J. A.; BURGESS, D. S. Plazomicin: a new aminoglycoside in the fight against antimicrobial resistance. **Therapeutic Advances in Infectious Disease**, v. 7, p. 2049936120952604, 2020. Disponível em: 10.1177/2049936120952604. Acesso em: 15 out. 2022.

CLIFFORD, K.M.; SELBY, A.R.; REVELES, K.R.; TENG, C.; HALL, R.G., 2ND.; MCCARRELL, J.; ALVAREZ, C.A. The risk and clinical implications of antibiotic-associated acute kidney injury: a review of the clinical data for agents with signals from the Food and Drug Administration's Adverse Event Reporting System (FAERS) Database. **Antibiotics**, v. 11, p. 1367, 2022. Disponível em: https://doi.org/10.3390/ antibiotics11101367. Acesso em: 31 out. 2023.

DAVIDSON, R. N.; DEN BOER, M.; RITMEIJER, K. Paromomycin. **Transactions of the Royal Society of Tropical Medicine and Hygiene**, v. 103, p. 653-660, 2009. Disponível em: 10.1016/j.trstmh.2008.09.008. Acesso em: 30 jun. 2022.

DOBREK, L. A synopsis of current theories on drug-induced nephrotoxicity. **Life**, v. 13, n. 2, p. 325, 2023. Disponível em: https://www.mdpi.com/2075-1729/13/2/325. Acesso em: 31 jul. 2022.

DOI, Y. Treatment options for carbapenem-resistant gram-negative bacterial infections. **Clinical Infectious Diseases**, v. 69, n. S7, p. S565-75, 2019. Disponível em: 10.1016/j.cmi.2019.10.017. Acesso em: 30 jun. 2022.

DRUSANO, G. L.; LOUIE, A. optimization of aminoglycoside therapy. **Antimicrobial Agents and Chemotherapy**, v. 55, n. 6, p. 2528-2531, 2011. Disponível em: 10.1128/AAC.01314-10. Acesso em: 15 out. 2022.

HODIAMONT, C. J.; VAN DEN BROEK, A. K.; DE VROOM, S. L.; JAN, M.; PRINS, J. M.; MATHÔT, R. A. A.; VAN HEST, R. M. Clinical pharmacokinetics of gentamicin in various patient populations and consequences for optimal dosing for gram negative infections: an updated review. **Clinical Pharmacokinetics**, v. 61, p. 1075-1094, 2022. Disponível em: https://doi.org/10.1007/s40262-022-01143. Acesso em: 30 jun. 2023.

HUMES, H. D. Aminoglycoside nephrotoxicity. **Kidney International**, v. 33, n. 4, p. 900-11, 1988. Disponível em: 10.1038/ki.1988.83. Acesso em: 31 jul. 2022.

JACKSON, J.; CHEN, C.; BUISING, K. Aminoglycosides: how should we use them in the 21st century? **Current Opinion in Infectious Diseases**, v. 26, n. 6, p. 516-25, 2013. Disponível em: 10.1097/QCO.0000000000000012. Acesso em: 30 jun. 2022.

LE, T. A.; HIBA, T.; CHAUDHARI, D.; PRESTON, A. N.; PALOWSKY, Z. R.; AHMADZADEH, S.; SHEKOOHI, S.; CORNETT, E. M.; KAYE, A. D. Aminoglycoside-related nephrotoxicity and ototoxicity in clinical practice: a review of pathophysiological mechanism and treatment options. **Advances in Therapy**, v. 40, n. 4, p. 1357-1365, 2023. Disponível em: https://link.springer.com/article/10.1007/s12325-023-02436-x. Acesso em: 30 set. 2023.

LEBEAUX, D.; FERNÁNDEZ-HIDALGO, N.; PILMIS, B.; TATTEVIN, P.; MAINARDI J-L. Aminoglycosides for infective endocarditis: time to say goodbye? **Clinical Microbiology and Infection**, v. 26, n. 6, p. 723-728, 2020. Disponível em: https://www.sciencedirect.com/science/article/pii/S1198743X19305531. Acesso em: 30 jun. 2022.

LEGGET, J. E. Aminoglycosides. *In:* BENNETT, J. E.; DOLIN, R.; BLASER, M. J**. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases**. 9th ed. Philadelphia: Elsevier Saunders, 2020. p. 305-317.

PRYTZ, K. L.; PRAG, M.; FREDLUND, H.; MAGNUSON, A.; SUNDQVIST, M.; KALMAN, J. Antibiotic treatment with one single dose of gentamicin at admittance in addition to a β-lactam antibiotic in the treatment of community-acquired bloodstream infection with sepsis. **PLoS ONE**, v. 15, n. 7, p. e0236864, 2020. Disponível em: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0236864. Acesso em: 31 jul. 2022.

LOPEZ-NOVOA, J. M.; QUIROS, Y.; VICENTE, L.; MORALES, A. I.; LOPEZ-HERNANDEZ, F. J. L. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. **Kidney International**, v. 79, p. 33-45, 2011. Disponível em: 10.1038/ki.2010.337.

NAGAI, J.; TAKANO, M. Molecular aspects of renal handling of aminoglycosides and strategies for preventing the nephrotoxicity. **Drug Metabolism and Pharmacokinetics**, v. 19, n.

3, p. 159-70, 2004. Disponível em: https://www.sciencedirect.com/science/article/abs/pii/S1347436715308156. Acesso em: 31 jul. 2022.

PAUL, M.; BENURI-SILBIGER, I.; SOARES-WEISER, K.; LEIBOVICI, L. Beta-lactam monotherapy versus beta-lactam aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. **British Medical Journal**, v. 328, p. 668, 2004. Disponível em: https://doi.org/10.1136/bmj.38028.520995.63. Acesso em: 30 jun. 2022.

PAUL M.; LADOR A.; GROZINSKY-GLASBERG S.; LEIBOVICI L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. **Cochrane Database of Systematic Reviews**, v. 1 (CD003344), 2014. Disponível em: 10.1002/14651858.CD003344.pub3. Acesso em: 30 jun. 2022.

REESE, R.; BETTS, R. Antibiotic use. *In*: **Reese and Betts' A Practical Approach to Infectious Diseases**. 5th ed. Lippincott Williams & Wilkins.; 2003:1065-1076.

ROSENBERG, C. R.; FANG, X.; ALLISON, K. R. Potentiating aminoglycoside antibiotics to reduce their toxic side effects. **PLoS ONE**, v. 15, n. 9, p. e0237948, 2020. Disponível em: https://doi.org/10.1371/journal.pone.0237948. Acesso em: 30 abr. 2022.

ROTHER, E. T. Systematic review X narrative review. **Acta Paulista de Enfermagem**, v. 20, n. 2, p. v-vi, 2007. Disponível em: 10.1590/S0103-21002007000200001 Acesso em: 30 mai. 2022.

SANTANA, L. A.; SANTOS, S. S.; GAZINEO, J. L. D.; GOMES, A. P.; MIGUEL, P. S. B.; GELLER, M.; SIQUEIRA-BATISTA, R. Plague: a new old disease. **Journal of Epidemiology and Public Health Reviews**, v. 1, p. 1-7, 2016. Disponível em: https://sciforschenonline.org/journals/epidemiology-public-health/JEPHR-1-128.php. Acesso em: 30 jun. 2022.

SCHECHTER, M. Princípios de antibioticoterapia. In: Schechter M, Marangoni DV. **Doenças infecciosas e parasitárias: conduta diagnóstica e terapêutica**. 2ª ed. Rio de Janeiro: Guanabara Koogan, 1998.

SIQUEIRA-BATISTA, R.; GOMES, AP. **Antimicrobianos: guia prático**. 3ª ed. Rio de Janeiro: Rubio, 2021.

SIQUEIRA-BATISTA, R.; ALVES, M. M. R.; LARA, M. A. G.; GOMES, A. P.; GAZINEO, J. L. D.; BRAGA, L. M. Penicillins: update for clinical practice. **Revista Médica de Minas Gerais**, v. 33, p. e-33209, 2023. Disponível em: https://rmmg.org/artigo/detalhes/4016. Acesso em: 30 set. 2023.

TAMMA, P. D.; AITKEN, S. L.; BONOMO, R. A.; MATHERS, A. J.; VAN DUIN, D.; CLANCY, C. J. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-

P. aeruginosa). **Clinical Infectious Diseases**, v. 75, n. 2, p. 187-212, 2022. Disponível em: 10.1093/cid/ciac268. Acesso em: 30 jun. 2023.

TAVARES, W. **Antibióticos e quimioterápicos para o clínico**. 4ª ed. São Paulo: Atheneu, 2020.

TEVYASHOVA, A. N.; SHAPOVALOVA, K. S**.** Potential for the development of a new generation of aminoglycoside antibiotics. **Pharmaceutical Chemistry Journal**, v. 55, n. 9, p. 860-875, 2021. Disponível em: 10.1007/s11094-021-02510-0. Acesso em: 15 mai. 2022.

TOMPKINS, K.; VAN DUIN, D. Treatment for carbapenem-resistant Enterobacterales infections: recent advances and future directions. **European Journal of Clinical Microbiology & Infectious Diseases**, v. 40, n. 10, p. 2053-2068, 2021. Disponível em: 10.1007/s10096-021-04296-1. Acesso em: 30 jun. 2023.

WAGENLEHNER, F. M. E.; CLOUTIER, D. J.; KOMIRENKO, A. S.; CEBRIK, D. S.; KRAUSE, K. M.; KEEPERS, T. R.; CONNOLLY, L. E.; MILLER, L. G.; FRIEDLAND, I.; DWYER, J. P. EPIC Study Group. Once-daily plazomicin for complicated urinary tract infections. **The New England Journal of Medicine**, v. 380, n. 8, p. 729-740, 2019. Disponível em: 10.1056/NEJMoa1801467. Acesso em: 31 out. 2022.

WANG, N.; LUO, J.; DENG, F.; HUANG, Y.; ZHOU, H. Antibiotic combination therapy: a strategy to overcome bacterial resistance to aminoglycoside antibiotics. **Frontiers in Pharmacology**, v. 13, p. 839808, 2022. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8905495/?report=reader. Acesso em: 30 jun. 2023.

YAN, K.; LIANG, B.; ZHANG, G.; WANG, J.; ZHU, M.; CA, Y. Efficacy and safety of plazomicin in the treatment of enterobacterales infections: a meta-analysis of randomized controlled trials. **Open Forum Infectious Diseases**, v. 29, n. 9, p. (9):ofac429, 2022. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9454024/. Acesso em: 30 jun. 2023.

Declaration of Interest
The authors declare that there is no conflict of interest

Financing
Own financing

Collaboration between authors
This article was written by Jorge Luiz Dutra Gazineo, Guilherme Fiorino Bissoli, Gustavo Canaan Barros Lima, Ramon Aragão Dutra Neto, Ranielle Bruno dos Santos e Renato Ismael Cordeiro de Souza, Andréia Patrícia Gomes, Adriano Simões Barbosa Castro, Luiz Alberto Santana e Rodrigo Siqueira-Batista, designed. All authors approved the final version of the text.