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Clinical relevance of therapeutic drug monitoring for amikacin and gentamicin

Relevância clínica do monitoramento terapêutico de fármacos para amicacina e gentamicina

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Abstract:

Aminoglycoside antibiotics (AG) are widely prescribed to treat severe bacterial infections in neonates, elderly, and critically ill patients. Considering the global increase in antimicrobial resistance, it is necessary to address this problem by optimizing available resources. Therapeutical drug monitoring (TDM) allows dose individualization and assists in preventing under or overdosage-related events. In this sense, the objective of this review was to analyze scientific evidence in the literature about the clinical importance of TDM for AG, access available data about its benefits, cover the main topics and provide an overview of this practice. PubMed and Science Direct databases were searched for: “therapeutic drug monitoring” and “aminoglycosides,” limiting the search to articles published between 2015 and 2022. In total, 26 articles were included in this review. TDM seems to be especially beneficial to elderly, neonates and critically ill patients, and target concentrations and sampling times are already well established, with the most recommended target being Cmax/MIC > 8. However, knowledge and training of the involved staff are essential to implement and interpret the TDM adequately.

Keywords: aminoglycosides, adverse effects, infection, antibiotics

Resumo:

Antibióticos aminoglicosídeos (AG) são amplamente prescritos no tratamento de infecções bacterianas graves em pacientes neonatos, idosos e críticos. Considerando o aumento global na resistência a antimicrobianos, é necessário o uso de estratégias para evitar este problema, otimizando os recursos disponíveis. O monitoramento terapêutico de fármacos (MTF) permite a individualização de dose e ajuda a prevenir eventos adversos relacionados a sub ou sobredosagem. Neste sentido, o objetivo desta revisão foi analisar as evidências científicas na literatura sobre a importância clínica do MTF para AG, abordando dados quanto aos seus benefícios, abrangendo os principais pontos relacionados a essa prática, fornecendo uma visão geral do assunto. As databases PubMed e Science Direct foram consultadas utilizando para a busca os termos: “therapeutic drug monitoring” e “aminoglycosides”, limitando para artigos publicados entre 2015 e 2022. Ao todo, 26 artigos foram incluídos nesta revisão. O MTF parece beneficiar especialmente os pacientes idosos, neonatos e críticos, com concentrações alvo e tempos de coleta bem estabelecidos, sendo que o alvo terapêutico mais recomendado é o Cmáx/CIM > 8. Porém, o treinamento e conhecimento da equipe envolvida é essencial para a implementar e interpretar o MTF adequadamente.

Palavras-chave: aminoglicosídeos, efeitos adversos, infecção, antibióticos

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INTRODUCTION

In the face of the growth in antimicrobial resistance and the reduction in the development of new antibiotics, the search for optimized antibiotic dosage regimens with better clinical results has increased in recent years. Therapeutic drug monitoring (TDM) is an alternative for optimizing adopted dosage regimens. With this practice, it is possible to adopt the most appropriate dosage, improving the clinical outcome of the treatment and reducing the probability of adverse events related to drug toxicity[1–4].

Aminoglycosides are bactericidal drugs indicated for the treatment of infections by gram-negative bacteria. They act on the 30s subunit of the bacterial ribosome, interrupting protein synthesis. Aminoglycosides present low plasma protein binding and predominantly renal elimination[5–7]. The pharmacokinetic parameters show high interindividual variability and may differ between patients, particularly in special populations[5,6,8,9]. Amikacin, gentamicin, tobramycin, and kanamycin are currently available aminoglycosides, with amikacin and gentamicin being the most prescribed[5,10]. These drugs are considered to have a concentration-dependent effect, the efficacy and toxicity are correlated with peak and trough blood concentrations, respectively[8,11]. The antimicrobial activity is mainly related to the ratio between maximum concentration (peak) and minimum inhibitory concentration (Cmax/MIC)[1,3].

Aminoglycosides such as amikacin, in association or not with other antimicrobials, are among the few available alternatives to treat severe, potentially fatal infections by multi-resistant microorganisms[5,12,13]. However, these drugs present a significant toxicity potential, so their dosage regimen requires attention to avoid complications such as ototoxicity and nephrotoxicity, especially in patients with impaired renal function[8,14]. Clinical studies have described the lack of ideal dosage models for aminoglycosides, mainly in specific populations such as neonate and elderly patients and critically ill patients with hemodynamic instability, septicemia, and organ failure[6,15,16].

In addition to the issues related to drug toxicity, the inappropriate use of antibiotics during the COVID-19 pandemic raises a concern regarding the spread of antimicrobial resistance in the long term. Therefore, reducing the inefficient use of antimicrobials and optimizing the therapy, when necessary, should be considered priorities[17]. In this context, this review

aimed to analyze the available evidence in the scientific literature on the use and clinical importance of therapeutic drug monitoring of the aminoglycosides amikacin and gentamicin and how it helps to increase clinical and microbiological outcomes and to decrease possible adverse effects. Additionally, this study describes some critical aspects of patients, dosage regimens, and the most adopted pharmacokinetics/pharmacodynamic targets.

METHODS

RESEARCH DESCRIPTION

This article is a narrative review of the available literature about therapeutic drug monitoring of aminoglycosides amikacin and gentamicin in clinical practice. The search was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA)[18]. This review is based both on prospective and retrospective studies, published between January 2015 and May 2022, presenting an overview of the most recent and relevant studies on the topic as well as the current practices, therapeutical targets and limitations of TDM for aminoglycosides.

IDENTIFICATION

The databases used for the search were PubMed and Science Direct, which are considered relevant to biomedical research worldwide. The search strategy adopted was the following: “therapeutic drug monitoring” AND “aminoglycosides”. Articles published between January 2015 and May 2022, in English or Portuguese were selected if relevant to the topic. Two reviewers were selected to carry out the systematic search for articles.

SELECTION AND ELEGIBILITY OF ARTICLES

To better organize and select the articles for this review, an electronic spreadsheet containing the following information was created in Microsoft Excel 2019: title, publication year, periodic name and database. The searched articles were subsequently evaluated based on their title and abstract. Those who seemed to fit in the objective of this review were selected for further reading of the full text to assess their eligibility for inclusion.

Regarding the eligible articles, some inclusion/exclusion criteria were adopted based on the proposed objectives. The inclusion criteria were: (1) full text available in the database, in English or Portuguese, (2) publication year between 2015 and 2022, (3) articles addressing the therapeutic drug monitoring of the aminoglycosides amikacin and gentamicin, assessing or not its pharmacokinetics and pharmacodynamics. Exclusion criteria were: (1) development and validation of analytical methodologies, (2) development of new formulations for antimicrobial drugs, (3) focus in resistance mechanism and/or drug mechanism of action, (4) focus in the treatment of tuberculosis or cystic fibrosis without TDM, (5) studies focused only in the development of pharmacokinetic models, (6) studies conducted in animals or in vitro, (7) reviews and case reports, (8) research based on questionnaires, paid articles, duplicated articles among databases, dissertations and theses.

RESULTS

The search in the selected databases resulted in 897 articles published between January 2015 and May 2022. After the exclusion of duplicates and analysis of remaining articles based on the established inclusion and exclusion criteria, a total of 26 were included in this review, as described in Figure 1.

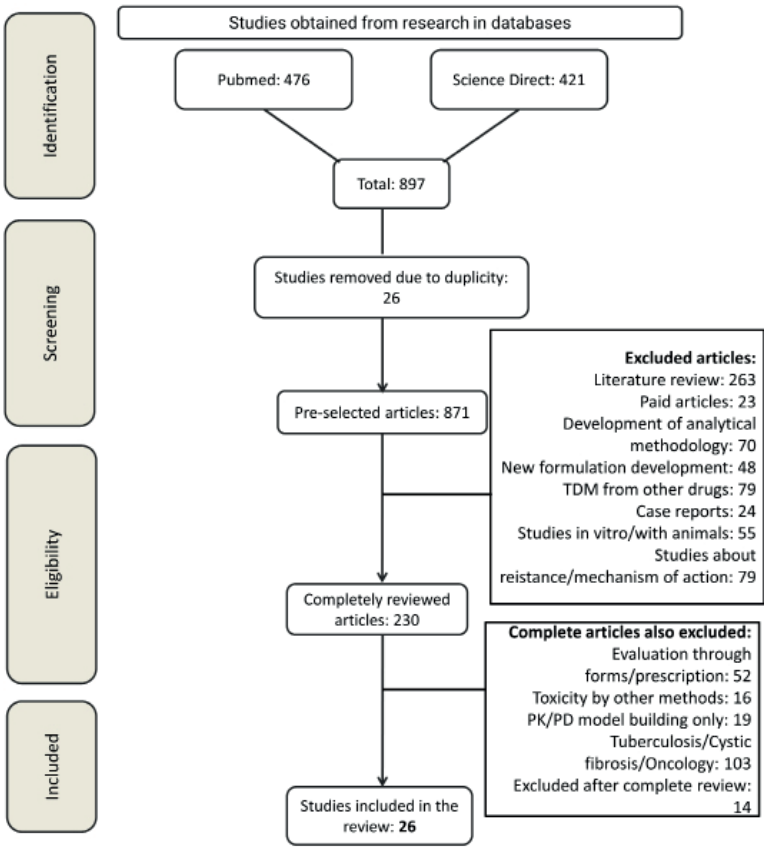

Figure 1. Flowchart PRISMA for identification and selection of the articles that compose this review.

The selected articles are presented and characterized in Table 1, which describes the study type, analytical methodology, dosage and adopted target values for plasmatic concentration. Of the 26 selected studies, 46.15% focused on amikacin TDM, 23.08% on gentamicin TDM, and 30.77% assessed TDM for both aminoglycosides. Regarding the patient population, pediatric patients were evaluated in 26.92% of the articles, most of which focused on neonates. Adult patients, critically ill or not, were evaluated in 65.38% of the studies, and only 2 (7.69%) of the reviewed articles focused on elderly patients.

Table 1: Summary of included studies characteristics.							
Author	**Patient characteristics**	**Study design**	**Antimicrobial**	**Analytical methodology**	**Dose**	**Therapeutic target**	**Amikacin and/ or gentamicin related results**
JAISWAL et al. (2022)	Adult patients (n=30)	Prospective pilot study	Amikacin	HPLC-UV	500-900 mg q24-72h	-	Cmax >15 mg/L in 83% and Cmin >5 mg/L in 37% of the patients
ROGER et al. (2021)	Adult ICU patients (n=931)	Prospective international cohort	Amikacin (614)*, gentamicin (303)* e tobramycin (14)*	-	Amikacin: 26mg/kg (IQR 21.9-29.4) q26.7h (IQR 23-45); Gentamicin: 5.6mg/kg (IQR 4.3-7.5) q24.8h (23-34)	Cmax/MIC ≥8; Cmin <2.5 mg/L (amikacin) and <0.5 mg/L (gentamicin)	Cmax/MIC >8 in 68% and Cmin above target in 71% of the TDM patients
KATO et al. (2021)	Elderly patients (age ≥70 years) (n=15)	Retrospective	Amikacin	FPIA (Roche Diagnostics, Japan)	200-2000mg q24/48/72h	Cmax/MIC ≥8; Cmin <4mg/L	Cmax/MIC >8 in 83.3% of the patients
BOYER et al (2021)	Critically ill patients receiving CRRT (n=303)	Multicentric, observational	Amikacin and gentamicin	Homogeneous particle-enhanced turbidimetric immunoassay (QMS Amikacin Assay Thermo Fisher Scientific)	20.2 mg/kg (amikacin) and 6.0 mg/kg (gentamicin), 1x/day	Cmax: 20-30mg/L (gentamicin) and 40-80 mg/L (amikacin); Cmin: 0.5-2.0 mg/L (gentamicin) and 2.5-5.0 mg/L (amikacin).	Amikacin median Cmax of 50 mg/L (IQR 43.7-76.6 mg/L) and CH24 of 9.3 mg/L (IQR 6.6-12 mg/L) Gentamicin median Cmax of 17.3 mg/L (IQR 13.2-22.5 mg/L) and CH24 of 2.3 mg/L (1.6-3.2 mg/L)

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Author	Patient characteristics	Study design	Antimicrobial	Analytical methodology	Dose	Therapeutic target	Amikacin and/ or gentamicin related results
SABUR et al. (2021)	Adult patients (n=49)	Retrospective cohort	Amikacin	-	8.9 mg/Kg q24h (IQR 8-10); 8.1 mg/ Kg 3x/week (IQR 7.3-9.2)	Cmax (daily dose): 25-30 mg/L; Cmax (3 doses/week): 30-35 mg/L;	Higher Cmax of 34.8 mg/L, 85.3% of measurements inside therapeutic range. Cmax of 25-30 mg/L daily doses and 30-35 mg/L for 3 doses/ weak regimens
RYAN et al. (2020)	Adult patients (n=47)	Retrospective	Amikacin	Immunoassay	13.9 mg/Kg/ day (range 4.3-25)	Cmax: 20-40 mg/L; AUC24 160-200 mg h/L	90% of suboptimal doses, target attainment: 44% AUC24, 71% Cmax and 94% Cmin. 66% of dose adjustments were appropriate
JAYAKUMAR et al (2020)	Urinary tract infection patients (age: 14-80 years) (n=125)	Prospective, observational	Amikacin	HPLC-tandem MS	15 mg/kg/ day	Cmax/MIC > 8	73.6% of patients with Cmax/MIC ≥ 8
DVOŘÁČKOVÁ et al. (2019)	Adult patients (n=63)	Prospective	Amikacin (27)*, gentamicin (36)*	-	-	Amikacin: Cmax >20 mg/L, Cmin <1 mg/L; Gentamicin: Cmax >10 mg/L and Cmin <2 mg/L	Group 1: target attainment of 70% in Cmax and 76% in Cmin; Group 2: target attainment of 54% in Cmax and 63% in Cmin

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Author	Patient characteristics	Study design	Antimicrobial	Analytical methodology	Dose	Therapeutic target	Amikacin and/ or gentamicin related results
ALHAMEED et al. (2019)	Adult patients (n=150)	Quasi-experimental (retrospective and prospective)	Vancomycin (142)*, Amikacin (1)* and gentamicin (7)*	-	-	-	Optimal initial dosing increase from 60% to 91%
DU TOIT et al. (2019)	Adult patients (n=103)	Observational retrospective	Gentamicin (65)* and amikacin (38)*	-	Amikacin: 500-1000mg q12h and 750-1000 mg q24h; Gentamicin: 80 mg q8h and 180-480 mg/ day	Cmax/MIC 8-10	20% of Cmin <1 mg/L (gentamicin) and 50% of Cmin <5 mg/L (amikacin)
ENDO et al. (2019)	Neonate premature patients (n=20)	Observational retrospective	Amikacin	KIMS (SRL Inc., Japan)	15 mg/Kg/day	Cmax 40-60 mg/L; Cmin <4 mg/L	Mean Cmax 42.5 mg/L (lower Cmax of 19.4 mg/L); mean Cmin of 7.86 mg/L (1.8 mg/L to 28.4 mg/L)
BEN ROMDHANE et al. (2019)	Routine TDM patients (n=88)	Retrospective	Amikacin e Gentamicin	EMIT (Siemens Healthcare Diagnostics)	Amikacin: 15.19 mg/Kg/day (range 4.82-33); Gentamicin: 3.0 mg/Kg/day (range 1.7-5.6)	Amikacin: Cmin <4 mg/L; Gentamicin: Cmin <1 mg/L	Intervention group: 60% with target concentrations on first TDM and 75% on second; Control group: 29% with target concentrations on first TDM and 31% on second

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Author	Patient characteristics	Study design	Antimicrobial	Analytical methodology	Dose	Therapeutic target	Amikacin and/ or gentamicin related results
SADEGHI et al. (2018)	Critically ill, elderly patients (age ≥65 years) (n=33)	Prospective, randomized, multicentric	Amikacin	ITA (UniCel DxC 880i Synchron Access)	15 mg/Kg and 25 mg/Kg q24h	Cmax/MIC >8, Cmax ≥64 mg/L	None of Group A and only 40% of Group B patients reached target Cmax
SINGU et al. (2018)	Adult female patients (n=29)	Observational, prospective	Gentamicin	PETINIA (ThermoScientific, USA)	240mg q24h	Cmax > 15 or 20 mg/L	Mean Cmax of 14.4 mg/L; Cmax ≥20 mg/L in 13.8% and Cmax ≥ 15 mg/L in 31% of the patients
VAN ALTENA et al. (2017)	Adult patients (age >17 years) (n=80)	Retrospective	Amikacin and Kanamycin	-	400 mg/day (IQR 400-568.2)	Cmax/MIC >20	Amikacin Cmax/ MIC of 31.2
HUGHES et al. (2017)	Neonate ICU patients (n=287)	Retrospective	Amikacin	-	Group 1: 15-18 mg/Kg q24, 36 or 48h; Group 2: 12-14 mg/kg q24 or 36h	Cmax 20-35 mg/L and Cmin <8 mg/L	Cmax: 37.7 mg/L and 28.5 mg/L, 34% and 84% of the patients with therapeutic levels; 65% and 12% with subtherapeutic levels
GONZALEZ et al. (2016)	Neonate patients (n=41)	Retrospective cohort	Gentamicin	Advia Centaur XP (Siemens Healthcare Diagnostics)	2,5-4 mg/Kg q8.24 or 36h	Cmin ≤1.5 mg/L	Mean Cmin of 1.7 mg/L (range 1.5 to 2.3 mg/L)
NAMAZI et al. (2016)	Adult patients (n=63)	Transversal	Amikacin	Turbidimeter AutoAnalyzer (Roche, Switzerland)	5-7.5 mg/kg q8h	Cmax: 15-30 mg/L and Cmin: 1-8 mg/L	38% attaining target Cmax and 45% attaining target Cmin

Table 1: Summary of included studies characteristics.

Author	Patient characteristics	Study design	Antimicrobial	Analytical methodology	Dose	Therapeutic target	Amikacin and/ or gentamicin related results
KOVAČEVIĆ et al. (2016)	Critically and non-critically ill patients (n=47)	Prospective	Amikacin and Gentamicin	KIMS (Roche/ Hitach)	Amikacin: 500 mg q8, 12 or 24h; Gentamicin: 2-5 mg/kg	Gentamicin: Cmin: <1 mg/L, Cmax: 5-10 mg/L (8-10 mg/L severe infections) e Amikacin: Cmin: 5-10 mg/L, Cmax: 20-30 mg/L (40 mg/L for life-threatening infections)	81.8% (critically ill) and 80% (non-critically ill) reached target concentration for amikacin. 88.9% (critically ill) e 77.3% (non-critically ill) reached target concentrations for gentamicin
VAN MAARSEVEEN et al. (2016)	Neonate patients (n=184)	Prospective, observational	Gentamicin	CMIA (Abbott Laboratories, Netherlands)	5 mg/Kg q36h	Cmax >8 mg/L; Cmin (estimated) <0.5 mg/L	91.3% with Cmax > 8 mg/L; 97.3% with Cmin <0.5 mg/L; 90.4% Cmax and Cmin within target range
FUCHS et al. (2016)	Premature pediatric patients (n=75)	Retrospective	Gentamicin	-	2.5-3 mg/Kg	Cmax 6-8 mg/L and Cmin 1-1.5 mg/L	Cmax: 5.7 mg/L (median, study group) and 5.6 mg/L (median, control group); estimated Cmin: 1.5 mg/L (median, study) and 1.6 mg/L (median, control)
BIALKOWSKI et al. (2016)	Pediatric patients (n=69)	Retrospective	Gentamicin	EMIT	7.4 mg/Kg/day (IQR 6.7-7.8) ≤10 years; 6.2 mg/Kg/day (IQR 5.5-7.1) ≥10 years	Cmax 25-40 mg/L; Cmin <2 mg/L; AUC(0-24) 70-90 mg/L*h	Cmax 20.6 mg/L; Cmin 0.002 mg/L; AUC(0-24) 63 mg/L*h (median, estimated values)

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Table 1: Summary of included studies characteristics.

Author	Patient characteristics	Study design	Antimicrobial	Analytical methodology	Dose	Therapeutic target	Amikacin and/or gentamicin related results
WHITE et al. (2015)	Adult patients (n=73)	Retrospective	Amikacin	ITA (Beckman Coulter, USA)	30-40 mg/kg critically ill patients; 24 mg/kg non critically ill patients;	Cmax/MIC ≥10 and AUC(0-24)/MIC ≥75	Mean Cmax: 100.9 ± 49.4 mg/L; mean Cmin 10.2 ± 12.5 mg/L; mean AUC24 600.2 ± 386.6 mg*h/L
SMITS et al. (2015)	Neonate patients (n=579)	Prospective	Amikacin	FPIA (kit, Abbott Laboratories, USA)	15-18 mg/kg q20,24, 30, 36, 42 or 48h	Cmin <3 mg/L and Cmax >24 mg/L	93.4% of the patients with Cmin ≤5 mg/L and 90.5% with Cmax > 24 mg/L
AL ZA'ABI et al. (2015)	Routine TDM patients (n=733)	Prospective transversal	Amikacin (84)*, gentamicin (218)*, others (431)*	KIMS (Roche/Hitachi Cobas systems)	-	-	AMK: 66.67% with subtherapeutic levels and 20.23% with supratherapeutic levels GENTA: 49.08% with subtherapeutic levels, 2.75% with supratherapeutic levels
PLAJER et al. (2015)	Adult patients (n=4523)	Retrospective, observational	Gentamicin	EMIT	3-7 mg/Kg (according to CLCR)	Cmax > 10 mg/L; Cmin <0.5 mg/L; AUC(0-24) 70-100 mg/L*h	Cmax: 17.3 mg/L (mean); Cmin: 0.3 mg/L (mean); AUC(0-24) 88 mg/L*h; 96% with Cmax >10 mg/L, 83% with Cmin <0.5 mg/L and 54% with AUC(0-24) between 70-100 mg/L

*Number of patients.
Abbreviations: ICU, intensive care unit; TDM, Therapeutic drug monitoring; Cmax/MIC, Maximum concentration over minimal inhibitory concentration; Cmin, minimal concentration; Cmax, maximum concentration; FPIA, Fluorescence polarization immunoassay; PK/PD, pharmacokinetic/pharmacodynamic; CRRT, Continuous renal replacement therapy; mg/L, milligrams per liter; 3x/week, three times a week; AUC24, area under curve from 24 hours; PETINIA, Particle-enhanced turbidimetric inhibition immunoassay; KIMS Kinetic interaction of microparticles in solution; EMIT, Enzyme multiplied Immunoassay; q24h, every 24 hours; ITA, Immunoturbidimetric assay; TINIA, Turbidimetric inhibition immunoassay; CMIA, Chemiluminescent microparticle immunoassay; AMK, amikacin; AUC0 – 24, area under curve form 0 to 24 hours; QMS, Quantitative microsphere system; HPLC-tandem MS, High-performance liquid chromatography tandem mass spectrometry; HPLC-UV, High-performance liquid chromatography with ultraviolet detector.

Of the reviewed articles, 84.61% described the adopted sampling time. Regarding peak plasmatic concentrations, all studies that presented this data used sample collection times up to two hours after infusion. Most studies used 30 minutes (42.31%) or 60 minutes (23.08%) after infusion. Only 2 (7.69%) articles used samples collected more than 60 minutes after infusion. The sampling time for trough concentrations was more heterogenic than for peak concentrations. Of 20 studies, 65% utilized samples collected between 0 and 1 hour before the next dose, with 50% proceeding with sampling 30 minutes or immediately before the start of the next dose infusion. Alternatively, 25% measured plasmatic concentrations 2 hours or more after the dose administration to estimate de Cmin. The analytical methodology for aminoglycosides quantification varied between the selected studies, with immunoassays being the most frequently used technique. Of the 18 articles that presented the analytical methodology, the most common techniques were: kinetic interaction of microparticles in solution (KIMS), enzyme-multiplied immunoassay (EMIT), and Immunoturbidimetric assay (ITA). Liquid chromatography methods were used in only two of the included articles.

For amikacin, dosage regimens ranged from 5 to 24 mg/Kg, with administration intervals ranging from every 8 hours (q8h) to 3 times a week. The most reported dose was 15 mg/Kg per day. Furthermore, there were reports of higher dose usage, ranging from 30 to 40 mg/Kg in critically ill patients[4,6,8,19–22]. Regarding gentamicin, doses ranged from 2 to 7.4 mg/Kg every 8 to 48 hours[16,23,24].

Of the 26 selected articles, 23 (88.46%) reported the used therapeutic target. In these, the targets adopted were Cmax, Cmin, Cmax/minimum inhibitory concentration (Cmax/MIC) ratio, area under the concentration-time curve from 0 to 24h/MIC(AUC(0-24)/MIC) ratio, and AUC (0-24). In the selected studies evaluating amikacin, Cmin was adopted in 70%

of the articles, with target concentrations ranging from <1 to 10 mg/L. Most of these articles used a target Cmin of 4 mg/L or less. Cmax was evaluated in 11 studies (55%), with concentrations ranging from 15 to 80 mg/L. The Cmax/MIC ratio was used by 35% of the studies, with Cmax/MIC≥8 ratio being the most adopted. The AUC (0-24)/MIC ratio was considered in only 2 studies (10%), with ratios greater than 75 being used as the target in both.

The subject of 14 selected studies was gentamicin. Cmin was the evaluated target in 71.43% of the studies, with the most adopted target of 1 mg/L or less. Cmax was used by 8 articles (57.14%), with target concentrations ranging from 5 to 40 mg/L. Cmax/MIC was considered in 14.28% of the studies, with ratios above 8 defined as the target. Lastly, 14.28% of the articles used the AUC (0-24) value as a therapeutic target for gentamicin TDM, considering concentrations of 70-90 mg/L and 70-100 mg/L.

DISCUSSION

Therapeutic drug monitoring stands out as a tool for dosage individualization, allowing for an adequate dose and better exposure to antimicrobials, favoring their therapeutic success[1,3]. Aminoglycosides have a low therapeutic index and wide intra and interindividual pharmacokinetic variability. Together with the relationship between plasma concentration and therapeutic or toxic effect, TDM is recommended for these drugs[8,25–27]. For a proper execution and interpretation of TDM, it is necessary to consider the right moment for blood sample collection, which should be performed after the steady state. These samples are usually collected at peak, the moment of maximum concentration (Cmax), which is attained after dose administration and generally related to treatment efficacy, and trough, corresponding to the minimum concentration (Cmin) and used in the evaluation of toxicity risk[20,28]. The most appropriate sampling time for a given drug depends on factors such as its elimination half-life and administration route. For aminoglycosides, it is recommended 30 minutes after the end of infusion for Cmax and 30 minutes before the next dose for Cmin[1].

Al Za'abi et al. (2015) observed that, in general, 71.5% of the samples for TDM were collected at inadequate times, with amikacin being the drug with the most inadequate samples (77.3% of samples). It was also mentioned that 59.2% of gentamicin samples were not collected at proper times, with a higher percentage of inadequate sample times in patients younger than 18 years. It is crucial to correctly record drug administration and

sample collection times, given that the proper interpretation of TDM results depends on this information. Errors in sample timing can lead to inadequate dose adjustments, potentially exposing patients to drug toxicity or therapeutic failure[29].

Aminoglycosides can be administered in multiple-daily dosing regimens, with 8 to 12 hours intervals, or every 24 to 72 hours in extended-interval regimens[19,30–32]. Recent international guidelines recommend amikacin doses of 3 mg/Kg every 72 hours up to 30 mg/Kg every 24 hours, mainly considering the patient's creatinine clearance[33]. The initial dose of 3 mg/Kg/day, divided into three administrations, has increased over the years, the European Committee on Antimicrobial susceptibility Testing (EUCAST) currently recommends a dose of 6 to 7 mg/Kg/day in a single dose[34]. Concerning special populations, dose adjustments for neonates are usually performed based on gestational age[9,35]. Critically ill patients may require higher doses to achieve established targets, with dose adjustments based on renal function in most cases[25,36].

According to a 2020 review and recommendations for TDM, target concentrations advised for amikacin peak values were related to efficacy, Cmax/MIC ≥ 8-10. On the other hand, Cmin values > 5 mg/L were related to toxicity, therefore, Cmin concentrations should be <2.5 mg/L. For gentamicin, a Cmax/MIC ≥ 8-10 or AUC (0-24)/MIC ≥ 110 are recommended, with target Cmin being < 0.5 mg/L since Cmin > 1 mg/L were related to toxicity[1]. Aminoglycosides pharmacokinetic variability is directly linked to changes in hemodynamic status, renal function, and fluid balance in these patients, impacting the volume of distribution (Vd) and clearance (Cl). Among the groups that present greater plasmatic levels variability for amikacin and gentamicin are neonates and critically ill patients with sepsis, septic shock, and/or burns[6,9,12,32,37].

Neonates were the study population in 7 articles[9,11,19,23,38–40]. Neonate dosage regimens are generally derived from those used in adults through extrapolations based on body weight[11]. In this sense, Cmin values greater than 1.5 mg/L for gentamicin are associated with toxicity in neonates. The retrospective study by Gonzalez et al. (2016) observed that the probability of raised gentamicin Cmin is higher for neonates with low postmenstrual age (PMA) and that none of the maternal characteristics analyzed is related to this probability[39]. In the study by Van Maarseveen et al. (2016), doses of 5 mg/kg every 36h with TDM

targeting Cmax >8 mg/L and estimated Cmin <0.5 mg/L in patients with early neonatal sepsis were evaluated. Of the 184 patients, 90% achieved Cmax and Cmin targets, indicating that this extended-interval dose regimen effectively achieved the therapeutic target. Significant associations were also observed between gestational age (GA) and body weight with Cmax and Cmin values, with gestational age being a predictor of underexposure, suggesting that patients with a lower gestational age need a higher dose to reach Cmax >8 mg/L9. The results of Gonzales et al. (2016) and Van Maarseveen et al. (2016) are contrasting because of the age differences of the populations addressed by the authors. Gonzales evaluated patients with a PMA range of 24 to 45 weeks, while Maarseveen did not evaluate patients with less than 32 weeks GA.

The TDM of amikacin was analyzed in three studies in neonates[11,19,40]. Although gentamicin is the most used in neonatal ICU, amikacin has increased due to bacterial resistance[40]. However, there is still discussion regarding dosage, especially considering the variation in the volume of distribution and renal function of neonates[19,40]. When comparing two dosing regimens for amikacin in neonatal ICU (NICU) patients, one based on literature data and the other based on local pharmacokinetic data, Hughes et al. (2017) observed that the group with dosing based on local pharmacokinetic data had mean Cmax (28.5 mg/L versus 37.7 mg/L) and percentage of patients with supratherapeutic levels (12% versus 65%) significantly lower than the other group. Furthermore, the dose based on local data showed a significant increase in patients with concentrations within the therapeutic target (84% versus 34%)[40].

In another study, Endo et al. (2019) evaluated 20 NICU patients receiving once-daily doses of 15 mg/Kg of amikacin. A trend towards high Cmin and ototoxicity was observed in patients with lower body weight, lower GA, and higher serum creatinine levels, indicating that these should be considered during TDM and dose adjustment[19]. Smits and colleagues (2015) obtained a high percentage of target attainment from TDM (90.5% of patients reached optimal Cmax) in their prospective evaluation of amikacin dosing in neonates based on the pharmacokinetic model11. TDM associated to popPK modeling favors the improvement of the dosage regimen, particularly for special populations, such as neonates.

In a prospective observational study with 29 obstetrics and gynecology patients receiving the standard local dose of 240 mg of gentamicin every 24h, only 31% reached the target Cmax

above 15 mg/L. These patients presented high disparity in body weight, and most received doses below the 5-7 mg/Kg recommended, indicating that the fixed-dose used is insufficient and that a dose adjusted by body weight would be a better alternative for this population[41].

Several authors emphasize the indication of amikacin and gentamicin TDM for adult patients, especially those in critical condition, such as severe sepsis or septic shock[8,36]. This recommendation may be related to the pathophysiological changes that impact the pharmacokinetics and pharmacodynamics of these antimicrobials. Furthermore, several studies have been conducted to help establish the best dosage regimens for these patients.

According to the literature, the main factors related to failure to reach pharmacokinetic-pharmacodynamic (PK/PD) targets for aminoglycosides in adult patients have been renal function, assessed by creatinine clearance (CrCl) or elevated serum creatinine concentrations, and the hemodynamic imbalances resulting from septic conditions[8,20]. In one study by Boyer et al. (2021), adult, critically ill, septic patients on continuous renal replacement therapy who received amikacin or gentamicin once daily were evaluated to determine the best interval between doses. The authors concluded that the adequate dose interval would be approximately 30 hours, depending on the initial dose administered[25]. These findings are similar to those described by other studies[42,43].

When evaluating amikacin therapy in critically ill, elderly patients, Sadeghi et al. (2018) found that the standard dose of 15 mg/Kg/day generated peak amikacin concentrations lower than 40 µg/mL, which were related to worse outcomes, more frequently. This finding corroborates White et al. (2015), who associated an amikacin dose of 15 mg/Kg/day with undesirable low concentrations[6,22]. It was also found that administering high doses of amikacin (at least 25 mg/Kg) to these patients is necessary to achieve a Cmax > 64 µg/mL and, consequently, the desired Cmax/MIC value > 8. However, to reduce toxicity, the interval between doses should be increased[6]. Boyer et al. (2021) also reported that the higher the intended pharmacodynamic target, the greater the dose and the interval between its administration, favoring treatment effectiveness and decreasing the risk of toxicity. However, it was stated that this approach needs to be prospectively studied[25].

In a study involving 15 elderly patients, Kato et al. (2021) observed that the achievement of a PK/PD target of Cmax/MIC ≥ 8 is directly related to renal function in these patients. A

decrease in physiological renal function is directly related to age and leads to a decrease in clearance and an increase in the volume of drug distribution. The authors suggested that for the elderly population, the dose regimen should be based on the CrCl and that a dosing regimen of 1800 mg every 48 or 72 hours, according to the renal function, is the most appropriate for Cmax/MIC ≥ 8 target[37].

Aminoglycosides elimination is directly affected by renal clearance[14,20]. Romdhane et al (2019) analyzed CrCl values associated with higher risks of amikacin or gentamicin toxicity though a ROC curve, obtaining a CrCl ≤ 41.66 mL/min as the threshold[8]. Other authors have also reported a correlation between aminoglycoside Cmin and serum creatinine and/or CrCl[7,20]

Nephrotoxicity and ototoxicity are the main reasons for aminoglycosides TDM indication[1,14]. In the study with 20 NICU patients, Endo et al. (2019) did not observe nephrotoxicity, although ototoxicity was reported in 20% of the patients treated with amikacin with Cmin >10 mg/L[19]. In another study, Van Altena et al. (2017) retrospectively addressed nephrotoxicity and ototoxicity in 54 patients receiving TDM-guided amikacin therapy. Nephrotoxicity was reported in 22.9% of patients, while ototoxicity was observed in 9.1% of patients. However, the only significant correlation was between dosage during a daily regimen and hearing loss in 8,000 Hz frequency[7]. Sabur and colleagues (2021) evaluated amikacin treatment in 49 patients and observed that only 12.2% presented hearing loss, although not severe. Regarding nephrotoxicity, it was observed in 23% of patients. Coadministration with nephrotoxic drugs increased the risk for serum creatinine elevation and decreased the probability of recuperation of renal function before the end of treatment. However, the authors stressed that these findings were based on a small number of patients[44]. Fuchs et al. (2016) retrospectively evaluated hearing loss during the first five years of life in children exposed to gentamicin, observing that it occurred in 25 out of 1582 children. However, they found no correlation between gentamicin exposure and hearing loss in the multivariate analysis. Most children were exposed to low doses and short treatment courses, indicating that, despite the risk, ototoxicity can be minimized with adequate dosing and TDM[38].

The impact of TDM on patients receiving a once-daily dose regimen with amikacin and gentamicin was accessed by Romdhane and colleagues (2019), 324 patients were included and separated into two groups, one group with patients who received TDM-guided

dosing (intervention) and another group with patients who did not (control). TDM-guided dose adjustments led to 75% of the patients archiving target Cmin in the intervention group versus 31% in the control group. It was also noted that patients with CrCl ≤41.66 mL/min had a significantly higher risk of toxic Cmin levels. Although the study focused on Cmin, the importance of TDM-guided dose adjustment for maintaining therapeutic concentrations and preventing toxicity is evident[8]. In another study, after evaluating amikacin TDM in 63 patients, Namazi et al. (2016) reported that nephrotoxicity was observed in 19% of the included patients. Therefore, it was recommended that data on plasmatic concentration and drug pharmacokinetics should be considered during dose selection and that TDM should be performed for this drug[21].

In a retrospective study with 4523 patients receiving extended interval gentamicin therapy, Plajer and colleagues (2015), observed that 6.6% of the patients experienced an increase in serum creatinine during a 7 to 14 days interval after the beginning of the treatment, but only 0.5% had irreversible damage. It was estimated that the risk for irreversible nephrotoxicity was 0.5 to 1.5% of the cases. It was also indicated that CrCl should be considered when choosing an administration interval, with an initial interval of 24h when patient CrCl ≥ 60 mL/min, 36h when CrCl is between 40 and 59 mL/min, and 48h when CrCl between 20 and 39 mL/min[24].

In another study, Bialkowski et al. (2016) accessed gentamicin pharmacokinetics in 69 pediatric patients with febrile neutropenia, finding that a 7.4 mg/Kg dose was not ideal since it resulted in subtherapeutic AUC(0-24) in 62% of the measures. Also, a higher clearance was observed in patients younger than 10 years, which can be related to failure in attaining therapeutic levels. It was estimated that doses of 10.8 mg/Kg (age ≤10 years) and 6.4 mg/Kg (age >10 years) would be needed to attain a target AUC of 80 mg/h*L, allowing for a better therapeutic efficacy[23].

Jayakumar and colleagues (2020) studied possible associations between amikacin pharmacokinetic parameters and healing time in patients with urinary tract infections. They found that patients who reached a PK/PD target of Cmax/MIC ≥ 8 had a lower mean time to heal than those who did not reach the target. Additionally, it was reported that Cmin could be used to predict nephrotoxicity, where higher serum creatinine was related

to higher Cmin[20]. This finding corroborates other reports in the literature being related to the decrease in renal clearance, which reduces drug elimination[6,8,22,24,37,41,45].

Critically and non-critically ill adult patients were compared in a study by Kovačević et al. (2016). They evaluated a small group of patients, finding that gentamicin peak concentrations were higher in critically ill patients. A similar trend was observed with amikacin, and the results were not statistically significant. Nevertheless, the number of patients with therapeutic levels was similar in both groups and drugs. Different from other studies, the authors concluded that TDM was unnecessary for these drugs since the local dosing protocol proved effective and secure for susceptible microorganisms[16].

When implementing TDM in the hospital routine, attention should be given to utilizing the results to optimize treatment effectively. Du Toit et al. (2019) reported that results are often underutilized due to a lack of concrete TDM guidelines, with a tendency for wrong or unreported sampling times[46]. This observation is reinforced by Namazi et al. (2016), which describe staff unawareness of TDM function in therapy improvement, in addition to the lack of attention to relevant microbiological data in the adequate prescription of aminoglycosides[21]. Other studies have also evaluated the effectiveness of TDM implementation. Al Za'bi et al. (2015) accessed TDM practice for several drugs in a school hospital. Sampling time was inadequate for 77.3% and 59.2% of amikacin and gentamicin samples, respectively. Subtherapeutic levels were observed in 66.7% and 49.1% of amikacin and gentamicin samples. It was also noted that intervention occurred in only 24.2% of the subtherapeutic levels cases against 76.9% of the supratherapeutic levels cases, indicating a greater concern of physicians with toxic levels[29]. Likewise, Muller et al. (2016) observed a predominance of lower than recommended doses corresponding to 40.3% of the included patients treated with aminoglycosides[28]. Ryan and colleagues (2021) also reported using lower than recommended doses, inadequate dose adjustments, and incorrect sampling time. Toxicity concern was considered the cause of the lower doses[47].

Administration of adequate doses is fundamental for treatment effectiveness and prevention of antimicrobial resistance. This pattern of below the ideal doses must be associated with toxicity concerns[28]. However, due to the increased risk of therapeutic failure, subtherapeutic levels should receive as much attention as supratherapeutic levels[29]. Thus,

improvements in routine TDM practice are recommended, such as the implementation of standard local guidelines and staff qualification to properly optimize the treatment[21,46].

The TDM interpretation by a pharmacist using a pharmacokinetics software improved the attainment of therapeutic levels for aminoglycosides in both Cmax and Cmin when compared to physician interpretation alone (70 and 76% versus 54 and 63%)[48], while the training of the clinical pharmacy staff resulted in a significant increase in optimal initial doses (60 to 91%)[49]. Showing the importance of multidisciplinary discussion in the adequate therapeutical management of routine TDM patients. Based on the studies evaluated in this review, 64.28% recommend, in one way or another, the improvement of aminoglycoside therapy through the implementation of routine TDM with standardized guidelines and qualified professionals in order to optimize treatment appropriately[21,46,50].

CONCLUSION

Although not yet routine in many locations, therapeutic drug monitoring of amikacin and gentamicin has been proven relevant. Given that elevated plasmatic concentrations and prolonged courses are related to adverse effects resulting from their toxicity. In this sense, TDM has been beneficial and recommended by groups of experts. However, it is necessary to train the involved team to know its usefulness and the appropriate management necessary for its application. Few studies could correlate the attainment of PK/PD targets with microbiological data, often due to empirical treatment. Nevertheless, clinical results were positive in those who did archive the established targets. Neonatal and critically ill patients benefit most from this practice, especially since they are the populations with the most significant interindividual pharmacokinetic variability.

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DECLARATION OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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