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Review Article

Impact of the use of macrolide antibiotics on bacterial resistance in non-fibrocystic bronchiectasis: a systematic review

Impacto do uso de antibiótico macrolídeos na resistência bacteriana em bronquiectasias não fibrocísticas: revisão sistemática

Impacto del uso de antibióticos macrólidos sobre la resistencia bacteriana en las bronquiectasias no fibroquísticas: revisión sistemática

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Corresponding author:
E-mail: daniferamos@gmail.com
Address: General Osório Street, s/nº, Health Campus, 2nd floor. Rio Grande, Rio Grande do Sul, Brazil.

Nadine Kinetz Funck[1]
Marcelle Oliveira Garcia[1,2]
Daniel Wenceslau Votto Olmedo[1,2]
Daniela Fernandes Ramos[1,2]

[1]Center for the Development of New Drugs (NUDEFA), School of Medicine, Federal University of Rio Grande (FURG), Rio Grande, Brazil.
[2]Postgraduate Program in Health Sciences (PPGCS), Federal University of Rio Grande (FURG), Rio Grande, Brazil.

ABSTRACT

Background and Objectives: bronchiectasis is a chronic respiratory disease characterized by irreversible bronchial wall dilation, mucociliary dysfunction, persistent cough, productive sputum and recurrent infections. The use of antibiotics is an essential part of the treatment of non-cystic fibrosis bronchiectasis, with macrolides being commonly used due to their anti-inflammatory properties and effectiveness in neutrophilic diseases. However, the frequent use of macrolides is concerning due to their potential to induce antimicrobial resistance. In this regard, this article assessed the impact of macrolide antibiotic therapy in non-cystic fibrosis bronchiectasis on the emergence of bacterial resistance. **Methods:** this is a descriptive systematic review, carried out in the PubMed, LILACS and SciELO databases, including all articles published until August 2020 that were available in Portuguese, English and/or Spanish, using the keywords "antimicrobial resistance" and "bronchiectasis". On the other hand, reviews, opinion articles and editorials were excluded as well as those works that did not investigate bacterial resistance, especially to macrolide antibiotics. **Results:** the review found five studies, all carried out between 2008 and 2016 in Australia, New Zealand and the Netherlands, that assessed the effects of macrolides in children and adults with bronchiectasis. Four were controlled clinical trials and one was a prospective cohort study. Although studies have shown that macrolides were effective in reducing exacerbations and improving lung function, they have also reported the development of macrolide resistance in some cases. This article emphasizes the need for cautious use of macrolides in the treatment of bronchiectasis unrelated to cystic fibrosis due to the potential for antimicrobial resistance.

Keywords: *Bronchiectasis. Drug Resistance, Microbial. Antimicrobials. Azithromycin.*

RESUMO

Justificativa e Objetivos: a bronquiectasia é uma doença respiratória crônica caracterizada por dilatação irreversível da parede brônquica, disfunção mucociliar, tosse persistente, expectoração produtiva e infecções recorrentes. O uso de antibióticos é parte essencial do tratamento de bronquiectasias não fibrose cística, sendo os macrolídeos comumente utilizados devido às suas propriedades anti-inflamatórias e eficácia nas doenças neutrofílicas. No entanto, o uso frequente de macrolídeos é preocupante, devido ao seu potencial em induzir resistência antimicrobiana. Nesse sentido, este artigo avaliou o impacto da antibioticoterapia macrolídeo em bronquiectasias não fibrose cística no surgimento de resistência bacteriana. **Métodos:** trata-se de revisão sistemática descritiva realizada nas bases de dados PubMed, LILACS e SciELO, incluindo todos os artigos publicados até agosto de 2020 que estivessem disponíveis em português, inglês e/ou espanhol, encontrados pelas palavras-chave "resistência antimicrobiana" e "bronquiectasia". Por outro lado, foram excluídos revisões, artigos de opinião e editoriais, e aqueles trabalhos que não investigaram a resistência bacteriana, especialmente a antibióticos macrolídeos. **Resultados:** a revisão encontrou cinco estudos, todos realizados entre 2008 e 2016 na Austrália, Nova Zelândia e Países Baixos, que avaliaram os efeitos dos macrolídeos em crianças e adultos com bronquiectasias. Quatro eram ensaios clínicos controlados e um era estudo de coorte prospectivo. Embora os estudos tenham demonstrado que os macrolídeos foram eficazes na redução das exacerbações e na melhoria da função pulmonar, também relataram o desenvolvimento de resistência aos macrolídeos em alguns casos. Este artigo enfatiza a necessidade do uso cauteloso de macrolídeos no tratamento de bronquiectasias não relacionadas à fibrose cística devido ao potencial de resistência antimicrobiana.

Descritores: *Bronquiectasia. Resistência Microbiana a Antibióticos. Antimicrobianos. Azitromicina.*

RESUMEN

Justificación y Objetivos: las bronquiectasias son una enfermedad respiratoria crónica caracterizada por dilatación irreversible de la pared bronquial, disfunción mucociliar, tos persistente, esputo productivo e infecciones recurrentes. El uso de antibióticos es una parte esencial del tratamiento de las bronquiectasias por fibrosis no quística, siendo habitual el uso de macrólidos por sus propiedades antiinflamatorias y su eficacia en las enfermedades neutrofílicas. Sin embargo, el uso frecuente de macrólidos es preocupante debido a su potencial para inducir resistencia a los antimicrobianos. En este sentido, este artículo evaluó el impacto de la terapia con antibióticos macrólidos en las bronquiectasias por fibrosis no quística sobre la aparición de resistencia bacteriana. **Métodos:** se trata de una revisión sistemática descriptiva, realizada en las bases de datos PubMed, LILACS y SciELO, que incluye todos los artículos publicados hasta agosto de 2020 que estaban disponibles en portugués, inglés y/o español, encontrados por las palabras clave "resistencia a los antimicrobianos" y "bronquiectasias". Por otro lado, se excluyeron revisiones, artículos de opinión y editoriales, y aquellos trabajos que no investigaran la resistencia bacteriana, especialmente a los antibióticos macrólidos. **Resultados:** la revisión encontró cinco estudios, todos realizados entre 2008 y 2016 en Australia, Nueva Zelanda y Países Bajos, que evaluaron los efectos de los macrólidos en niños y adultos con bronquiectasias. Cuatro fueron ensayos clínicos controlados y uno fue un estudio de cohorte prospectivo. Aunque los estudios han demostrado que los macrólidos fueron eficaces para reducir las exacerbaciones y mejorar la función pulmonar, también han informado el desarrollo de resistencia a los macrólidos en algunos casos. Este artículo enfatiza la necesidad de un uso cauteloso de macrólidos en el tratamiento de bronquiectasias no relacionadas con la fibrosis quística debido al potencial de resistencia a los antimicrobianos.

Palabras Clave: *Bronquiectasias. Farmacoresistencia Microbiana. Antimicrobiano. Azitromicina.*

INTRODUCTION

Bronchiectasis is a chronic and disabling lung disease marked by bronchial wall permanent and abnormal expansions. This condition results in compromised function of mucociliary clearance mechanisms, leading to a persistent cough, copious mucus production, and frequent respiratory infections. In addition to making breathing difficult, bronchiectasis can cause fatigue, chest pain and significantly reduce patients' quality of life.[1-2] It can be caused by various etiologies, such as autoimmune diseases (rheumatoid arthritis and Sjögren's syndrome), severe infections (tuberculosis and bacterial pneumonia), genetic abnormalities (cystic fibrosis and primary ciliary dyskinesia) and acquired diseases.[3]

The use of antibiotics is an important part of the treatment for non-fibrocystic bronchiectasis.[3] Several classes of antibiotics and formulations tested have already established their role in providing clinical benefits, especially in patients with an exacerbator profile.[3] An exacerbator profile is defined as a worsening of respiratory symptoms treated with oral or intravenous antibiotics.[4] Macrolides are widely used antibiotics in the treatment of bronchiectasis due to their ease of administration, anti-inflammatory properties, and efficacy in cystic fibrosis and other neutrophilic diseases.[4] Moreover, macrolides have the advantages of high plasma concentration, long half-life, and broad antimicrobial spectrum.[4] All of this provides justification for this class of antibiotics to be used as maintenance therapy in patients with non-fibrocystic bronchiectasis and for prevention of exacerbations.[5] Macrolides inhibit protein production by reversibly binding to the 50S ribosomal subunit of susceptible microorganisms, blocking mRNA translation without interfering with nucleic acid synthesis. However, the widespread use of these antibiotics has inevitably led to the spread of resistant strains.[6] The two most common mechanisms of resistance are excretion of the drug from the cell and modification of the drug target site. Resistance can occur in long-term treatment prescriptions, especially in chronic diseases such as cystic fibrosis and bronchiectasis, where frequent and continuous use of macrolides can select resistant strains.[4] Developing more details about these mechanisms and the clinical conditions under which resistance is most likely helps to elucidate the complexity of the problem and the need for appropriate management strategies to prevent antimicrobial resistance. [4,6]

Currently, antimicrobial resistance is considered a global threat to health and development according to the World Health Organization (WHO).[8] Accordingly, it is known that this phenomenon leads to increased costs and overload of health systems, since patients infected with resistant pathogens are hospitalized for longer and use more expensive drugs.[9-10] Recently, due to the Covid-19 pandemic, many antibiotics have been prescribed, without taking into account the potential for increased antimicrobial resistance, which generates a global scenario of uncertainty regarding the future effectiveness of the antibiotics that exist today.[8] Therefore, this article aimed to assess the impact of antibiotic therapy with macrolides in non-fibrocystic bronchiectasis on the emergence of bacterial resistance through a systematic review.

METHODS

Experimental design and selection criteria

This is a descriptive systematic review that adopted the Preferred Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Therefore, the following items were considered: eligibility criteria; exclusion criteria**;** information source and search strategy; selection of studies; and data collection.

Eligibility and exclusion criteria

In this study, were defined as eligibility criteria: i) experimental articles dealing with non-cystic fibrous bronchiectasis, regardless of the age group; ii) articles showing results regarding antimicrobial resistance to macrolides; iii) articles available in Portuguese, English and/or Spanish published until August 2020 in the PubMed, LILACS and SciELO databases. Reviews, editorials and personal views as well as articles not available in full and/or that did not address macrolide resistance involving patients with non-cystic fibrosis bronchiectasis were excluded.

Article search and selection strategies

Study selection, data collection, risk of bias in individual studies were carried out during the period from July to August 2020. Through the keywords "antimicrobial resistance" and "bronchiectasis", using the Boolean operator "AND". So, 295 articles were found; among these, 47 were selected for full reading (by two researchers, independently, reducing the risk of bias) based on the title. However, 42 articles were discarded due to eligibility criteria, resulting in five articles for analysis (Figure 1).

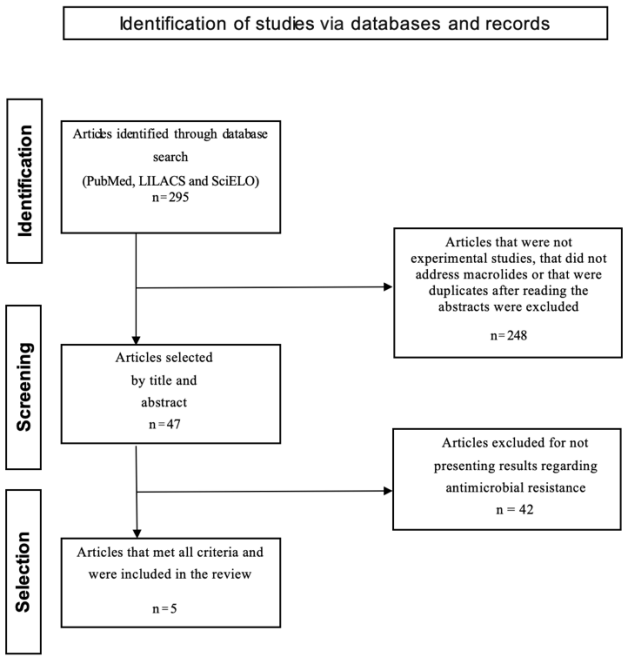

Figure 1. Identification of studies via databases and records.

RESULTS AND DISCUSSION

Among the five selected studies, four were placebo-controlled clinical studies and a prospective cohort study.[9–13] Three studies assessed the effects of macrolides in children.[11–13] All clinical trials, in turn, were conducted between 2008 and 2016 involving the population of Australia, New Zealand and the Netherlands. Important information about these studies is shown in the following table (Table 1).

Table 1. Clinical and prospective cohort studies evaluating the effects of macrolides in children and adults in Australia, New Zealand and the Netherlands (2008-2016).

Authors	Experimental design	Methods	Main results
Serisier *et al*. (2013)	Placebo-controlled clinical trial from 2008 to 2011 at an Australian university hospital	Oral erythromycin (400 mg, twice daily) or placebo	Oropharyngeal swab: erythromycin increased the proportion of macrolide-resistant commensal *Streptococcus*
Altenburg *et al*. (2013)	Placebo-controlled clinical trial in 14 hospitals in the Netherlands between 2008 and 2010	Oral azithromycin (250 mg, once a day) or placebo	Sputum sample: 88% of pathogens became resistant to macrolides in the azithromycin group, compared to 26% of pathogens in the placebo group
Valery *et al*. (2013)	Placebo-controlled clinical trial between 2008 and 2010 in Australia and New Zealand	Oral azithromycin (30 mg/kg, maximum of 600 mg) or placebo for 12 to 24 months	Nasal swab: increased carriage of azithromycin-resistant bacteria in the azithromycin group (7-fold higher odds)
Goyal *et al*. (2018)	Placebo-controlled clinical trial in Australia and New Zealand from 2012 to 2016	Azithromycin (5 mg/kg) or amoxicillin (22.5 mg/kg twice daily) for 21 days	29% in the amoxicillin group and 80% in the azithromycin group carried azithromycin-resistant organisms
Hare *et al*. (2013)	Prospective cohort study in Australia and Alaska from 2004 to 2008	Indigenous children from Australia (n = 79) and Alaska (n = 41) divided according to the use of azithromycin: no azithromycin in the 2-weeks preceding swab collection at any of the study visits; Azi-Infrequent - azithromycin preceding 1–50% of study visits; and Azi-Frequent - azithromycin preceding >50% of study visits	Nasopharyngeal swab: macrolide resistance was higher in Australia, and frequent use of azithromycin coincided with increased carriage of macrolide-resistant *S. pneumoniae*, *H. influenzae* and *S. aureus*

Legend:* *H. influenzae: Haemophilus influenzae; S. aureus: Staphylococcus aureus.*

Only one study assessed the emergence of erythromycin-resistant commensal *Streptococcus* in an oropharyngeal sample ($p<0.001$). All others focused on azithromycin as the macrolide of choice, demonstrating a significant relationship between different administration protocols of this antimicrobial and the increase in resistant microorganisms in sputum and nasopharynx samples. Thus, through an oropharyngeal smear for *Streptococcus* culture and macrolide sensitivity test, it was possible to show that the use of erythromycin significantly increased the proportion of *Streptococcus* resistant to macrolides (27.7% vs 0.04% or placebo; $p < 0.001$).[22]

Despite the increase in resistant pathogens, the use of erythromycin reduced the number of exacerbations (76 exacerbations per year for the erythromycin group *vs* 114 for the placebo group; $p = 0.003$).[11] This study emphasized the need to assess both the advantages and disadvantages of using this treatment. Although it may improve quality of life by reducing exacerbations, on the other hand, it may induce the emergence of resistant bacteria.[11] The resistance hypothesis suggests that while erythromycin has clinical benefits, continuous use may lead to the selection of resistant microorganisms. Bacteria exposed to antibiotics on a sublethal level may develop resistance mechanisms such as altering the antibiotic's target, activating the drug's enzyme, or altering the flow channels. While erythromicin may alleviate symptoms and improve patients' quality of life, indiscriminate use may contribute to a larger public health issue: the spread of drug-resistant pathogens.

On the other hand, in 2013, Altenburg *et al*. found comparable resistance patterns between groups (35% macrolide resistance among patients in the azithromycin group *vs* 27.5% in patients in the placebo group). However, during treatment, among patients receiving azithromycin, 88% of microorganisms became resistant to macrolides, compared to 26% in the placebo group ($p = 0.001$). Among the most frequently isolated microorganisms, *Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus, Moraxella catarrhalis* and *Haemophilus parainfluenzae* stand out, which together comprised 87% of the total number of pathogens, 75% of which were tested for resistance to macrolides.[11] In addition to the bronchiectasis, this class of antimicrobial agents has also been recommended as the first line for the treatment of community-acquired pneumonia, which may impact the emergence of resistant microorganisms (commensals or pathogens) not only in exacerbation episodes in patients with non-cystic fibrosis bronchiectasis, but also in other infectious episodes that affect this group of patients. Therefore, it is indicated that the use of macrolides as maintenance therapy occurs only in those patients who have three or more annual exacerbations.

Regarding the action of azithromycin in reducing pulmonary exacerbations, a multicenter, double-blind, randomized controlled trial conducted in Australia demonstrated that the group that received azithromycin was less prone to pulmonary exacerbations.[13] However, the chances of boosting bacterial resistance to azithromycin were seven times greater in the azithromycin-treated group than in the control group.

Valery *et al*. raised concerns about the long-term use of azithromycin in indigenous children with bronchiectasis unrelated to cystic fibrosis or chronic pulmonary. The prolonged use of azithromycin for patients with chronic lung diseases should be carefully considered, because, despite its advantages of improving lung function and decreasing disease exacerbations, it may lead to negative outcomes, associated with adverse effects such as hearing impairment, and the emergence of bacterial resistance in isolates from treated patients, which, in addition to decreasing bacterial colonization (of pathogenic microorganisms or microbiota), may impact the restriction of antibiotic use in future infectious processes. The study found that the possibility of bacterial resistance to azithromycin compromises treatment efficacy and can lead to more difficult-to-treat infections. Continuous use of azithromycin leads to the selection of resistant bacteria, which is exacerbated by mechanisms such as ribosome modification. As a result, it is critical to balance its use with microbiological surveillance and alternative strategies, such as antibacterial rotation cycles and antimicrobial management programs. At the same time, only two of the 12 children participating in the study who were identified as colonized with azithromycin-resistant *S. pneumoniae* at the last study visit already had colonization with this resistant microorganism at the beginning of the study (both in the azithromycin group), allowing to hypothesize that the continuous use of this macrolide (azithromycin - 30 mg/kg once a week for up to 24 months) may have been the booster of the resistance that emerged in these isolates at the end of the assessments.[13]

Considering the potential of antimicrobial agents in reducing exacerbations and their possible intervention in the emergence of resistant pathogens, a clinical trial carried out between 2012 and 2016, in three Australian hospitals and one New Zealand hospital, compared the daily oral use for 21 days of azithromycin and amoxicillin-clavulanate. All exacerbations resolved by day 21 of treatment in 77.3% of children receiving amoxicillin-clavulanate and 76.8% of those receiving azithromycin. Furthermore, the median time to resolution of exacerbations was four days shorter in the amoxicillin-clavulanate group than in the azithromycin group. Thus, it is evident that the macrolide does not play a fundamental and irreplaceable role in reducing the number and duration of exacerbations.[14]

Also, considering the exposure of colonizers to antimicrobial agents, the authors highlighted the identification of 74 pathogens in the nasal swabs of individuals recruited for the study, namely *H. influenzae, S. pneumoniae, M. catarrhalis* and *Staphylococcus aureus*. The bacteriological profile of nasal swabs, including carriage of azithromycin-resistant organisms, was similar in both treatment groups at the onset of an exacerbation. Of the children whose swabs still contained pathogens on day 21, 4/14 (29%) in the amoxicillin-clavulanate group and 8/10 (80%) who received azithromycin carried azithromycin-resistant organisms. Even though the profile of azithromycin-resistant *S. aureus* isolates in both treatment groups did not change over the study period, bacterial resistance was more common in the group that used azithromycin.[14]

The authors propose that macrolides have been used to treat other community-acquired infectious processes, which would support the presence of resistant respiratory bacterial pathogens at the beginning of the study.[14] Specifically regarding azithromycin-resistant *S. aureus*, it should also be highlighted that these microorganisms remain resistant even after antibiotic therapy is discontinued. In addition to this, studies indicate the presence of resistant *S. aureus* in local and invasive infections among indigenous children as a whole.

In a prospective cohort study, it was reported that many physicians in Australia routinely prescribe azithromycin (often long-term) to children with bronchiectasis, while in Alaska this practice is uncommon, because macrolide resistance was significantly higher in Australian children compared to those from Alaska.[15] They hypothesized that the two populations would differ in their nasopharyngeal transport of potential respiratory bacterial pathogens and antibiotic resistance genes in these microorganisms. They suspect that because of variations in how antibiotics are prescribed (e.g., frequency, duration, and choice of antibiotic), the two populations may have significant differences in both colonization by respiratory pathogens and the prevalence of resistant bacterial strains. [15]

About a quarter of the children involved in the study had respiratory exacerbations, and both those in Alaska and Australia had *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* and *Staphylococcus aureus* colonizing their nasopharynx. On the other hand, unlike the results found in relation to colonization by *S. pneumoniae* which remained stable over time, Alaska and Australia differed in terms of persistence with decline among carriers of *M. catarrhalis* in Alaska children and *H. influenzae* in

Australian children.[15] The authors are comparing the differences in the persistence of colonization by different respiratory pathogens among children in Alaska and Australia across time. The researchers found that whereas *S. pneumoniae* (a common respiratory pathogen) remained stable in both populations, there were notable differences in the persistence of other pathogens. In Alaska, *M. catarrhalis* colonization decreased over time, while in Australia, *H. influenzae* colonization decreased among children. This difference may reflect differences in environmental, genetic, immune, or health practices between the two populations, affecting these pathogens' ability to remain in the respiratory tract over time.[15]

Therefore, in order to investigate the cumulative effect of repeated and prolonged exposure to long-term azithromycin on bacterial transport and resistance, Australian children were divided into three groups based on the frequency of azithromycin use during the study period (no use, use for up to half of the assessment time, use for more than 50% of study visits).[15] Thus, none of the assessed microorganisms showed resistance to beta-lactams, but resistance to macrolides in carriers of *S. pneumoniae* and *S. aureus* was significantly higher in Australian children compared to those from Alaska. This suggests that antibiotic prescribing practices, health policies, or other regional factors may have contributed to a greater selective pressure that favors the development of macrolide resistance in Australian children. All *H. influenzae* isolates from Alaskan children and 80% of Australian children were susceptible to macrolides, with resistance to isolates of *S. pneumoniae*, *H. influenzae*, and *S. aureus* tending to be higher in the group that used azithromycin frequently. However, *S. pneumoniae* resistance increased throughout the study, regardless of the type of exposure to azithromycin.[15] As a result, the authors suggest that bacterial resistance is being influenced by both antibacterial use and other epidemiological dynamics.

Thus, all studies report a significant increase in resistant microorganisms compared to the placebo group when at least one macrolide was administered (the ones used in these studies being azithromycin and erythromycin), mainly related to gram-positive pathogens, as in the case of *Staphylococcus aureus* and *Streptococcus pneumoniae.*[11,15]

This scenario has often been reported for the control of exacerbations in other diseases, such as what has been pointed out since the onset of Covid-19, in which the use of azithromycin and ceftriaxone was reported in over 68% of individuals.[14] In addition, the lack of clear evidence for the beneficial effects of macrolide use both in the pandemic and in bronchiectasis has already been frequently documented by health teams. [17-18]

The increase in macrolide-resistant *S. pneumoniae* was present in two studies [13,15], further highlighting the possible unexpected and undesirable effects of using these antimicrobial agents, including the fact that they are often recommended as first-line agents for the treatment of community-acquired pneumonia (CAP). Thus, macrolide resistance may be a potential cause of treatment failure in patients with CAP.[13,15] Resistance to macrolides in CAP, as described in the articles, occurred due to frequent and inadequate use of these antibiotics, which promoted the selection of resistant bacteria. This resistance compromises treatment efficacy and increases the risk of therapeutic failure and clinical complications.

Azithromycin is the most prescribed macrolide in clinical practice, and its longer half-life favors the dosage (3 times a week).[19] According to the Brazilian consensus on non-cystic fibrosis bronchiectasis, the use of azithromycin is indicated through continued therapy of 6-12 months for patients with bronchiectasis and at least two exacerbations per year, or those with a history of severe exacerbation, primary or secondary immunodeficiency, excluding patients with active infection by non-tuberculous mycobacteria.[3]

On the other hand, these therapeutic practices provide long periods of subinhibitory concentrations that increase the risk of developing antimicrobial resistance by modulating the expression of virulence and pathogenicity genes as well as efflux pumps, especially in gram positives. Moreover, the emergence of resistant strains increases the risk of its transmission to other individuals in the community. [13,19-22]

Therefore, the clinical benefits need to be balanced against the risk of antimicrobial resistance, since the macrolide will not always be the best option as a rescue antimicrobial in exacerbation crises, and the increase in microbial resistance will lead to greater morbidity and mortality of the community as a whole, especially in risk groups, such as children and adults, who have been the main individuals referred in studies of bronchiectasis.[5,14]

Even with the worrying situation of the emergence of microbial resistance, which according to government agencies will be the next global epidemic, there have been few studies involving this topic, especially in patients with bronchiectasis, where the infection still appears to be only yet another event in the vicious cycle of the disease. Therefore, one of the main limitations found in this review was, in addition to the lack of studies, the lack of articles highlighting the resistance associated with the prophylactic or therapeutic use of macrolides in recent years. Therefore, the urgent need to assess patients' clinical conditions and their prognostic outcomes beyond the underlying chronic disease is evident.

The medical community needs to develop an approach to the treatment of non-fibrocystic bronchiectasis that

takes into account not only the immediate benefits to individuals, but also the risks to the wider community, and prognostic outcomes that do not involve recurrent infections with impossibility of cure.[22]

CONCLUSION

Bronchiectasis causes bronchial wall dilation and mucociliary dysfunction, leading to recurrent infections, cough, and sputum. Macrolides are effective antibiotics in the treatment of non-fibrocystic bronchiectasis, but their frequent use can lead to antimicrobial resistance. Studies conducted in Australia, New Zealand and the Netherlands between 2008 and 2016 found that macrolides, particularly azithromycin, can increase the emergence of resistant microorganisms. Therefore, careful monitoring is required when using macrolides to treat non-cystic fibrous bronchiectasis.

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AUTHORS' CONTRIBUTIONS

Nadine Kinetz Funck contribuiu para a pesquisa bibliográfica, redação do resumo, introdução, metodologia, discussão, interpretação e descrição dos resultados, elaboração de tabelas, conclusões e revisão. **Marcelle Oliveira Garcia** contribuiu com revisão crítica relevante do conteúdo intelectual, correção e aprovação final da versão a ser publicada. **Daniel Wenceslau Votto Olmedo** contribuiu na análise e interpretação dos dados. **Daniela Fernandes Ramos** foi responsável por todos os aspectos do trabalho na garantia da exatidão e integridade de qualquer parte da obra.

Todos os autores aprovaram a versão final a ser publicada e são responsáveis por todos os aspectos do trabalho, incluindo a garantia de sua precisão e integridade.

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