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Macrolide treatment in pediatric non-cystic fibrosis bronchiectasis: A meta-analysis

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Abstract

Objective: This meta-analysis aims to systematically review and synthesize the available data on long-term macrolide treatment for NCFB in children.

Materials and methods: On December 2, 2023, we conducted a comprehensive search across multiple databases, including PubMed, Cochrane Library, Embase, Web of Sciences, and SCOPUS. There were no restrictions on language. The search terms used were "Macrolides," "Azithromycin," "Clarithromycin," "Roxithromycin," "Erythromycin," "Bronchiectasis," "Kartagener syndrome," and "Ciliary motility disorders." A total of 4 RCTs were included.

Results: A total of 92 patients in Macrolid group and 87 patients in control group were included in this meta analysis. Despite variations in macrolide preparations, long-term macrolide use significantly reduced the frequency of acute exacerbations in bronchiectasis (I2=0%) (OR: 0.30, 95% CI: 0.10 to 0.87; p=0.03). The findings showed that long-term macrolide treatment significantly reduced the mean exacerbations per patient (I2=84%; WMD -1.40, 95% CI: -2.26 to -0.54; p=0.001). The results indicated no significant difference in the frequency of exacerbation-related admissions between the azithromycin group and the control group (OR: 0.28, 95% CI: 0.07 to 1.11; p=0.07). The results showed no significant difference in FEV1 between the macrolide treatment group and the control group (I2=80%; WMD 2.21, 95% CI: -2.44 to 6.87; p=0.35). The results indicated no significant difference in the changes of FEV1% predicted before and after treatment between the macrolide group and the control group (I2=0%; WMD 2.19, 95% CI: -2.80 to 7.19; p=0.39).

Conclusions: This meta-analysis reveals that long-term macrolide treatment, spanning 3 to 24 months, significantly reduces the frequency of exacerbations in pediatric NCFB.

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Introduction

Bronchiectasis, a chronic respiratory condition characterized by irreversible dilation and damage to the bronchial walls, leads to significant morbidity in affected individuals (1). While traditionally associated with cystic fibrosis (CF), non-cystic fibrosis bronchiectasis (NCFB) is increasingly recognized as a significant health concern, particularly in pediatric populations. NCFB in children often results from recurrent respiratory infections, immune deficiencies, and other underlying conditions that impair mucociliary clearance and lead to chronic bacterial colonization and inflammation (1-3).

The management of NCFB aims to reduce the frequency of exacerbations, improve quality of life, and preserve lung function (3,4). Among the various treatment strategies, long-term macrolide antibiotics have garnered attention for their dual antibacterial and anti-inflammatory properties (5-7). Macrolides, such as azithromycin and clarithromycin, have been shown to reduce the frequency of exacerbations and improve clinical outcomes in adults with bronchiectasis (9,10). However, the efficacy and safety of long-term macrolide therapy in children with NCFB remain areas of ongoing investigation (9,11).

Several randomized controlled trials (RCTs) and observational studies have explored the use of long-term macrolides in pediatric NCFB patients (12-15). These studies suggest potential benefits, including reduced exacerbation rates, improved pulmonary function, and enhanced quality of life. Nevertheless, concerns regarding antibiotic resistance, potential side effects, and the optimal duration of therapy necessitate a thorough evaluation of the existing evidence.

This meta-analysis aims to systematically review and synthesize the available data on long-term macrolide treatment for NCFB in children.

Materials and methods

Search strategy

On December 2, 2023, we conducted a comprehensive search across multiple databases, including PubMed, Cochrane Library, Embase, Web of Sciences, and SCOPUS. There were no restrictions on language. The search terms used were "Macrolides," "Azithromycin," "Clarithromycin," "Roxithromycin," "Erythromycin," "Bronchiectasis," "Kartagener syndrome," and "Ciliary motility disorders."

Eligibility criteria

This meta-analysis included randomized controlled trials (RCTs) that examined the effects of macrolide treatment lasting more than 4 weeks, compared with placebo or no intervention, for the long-term management of stable bronchiectasis in infants, children, and adolescents under 18 years of age. Studies involving ciliary motility disorders, including Kartagener syndrome, were also included. RCTs involving children with bronchiectasis associated with cystic fibrosis and adult patients were excluded from the analysis. Additionally, studies with insufficient treatment durations were not considered.

Data extraction

Data extraction and analysis were conducted independently by two reviewers. Initially, the titles and abstracts of de-duplicated studies were screened by both reviewers to identify relevant studies. Any discrepancies were resolved through discussion. Subsequently, the full texts of the selected articles were independently reviewed again by the same two reviewers. Data extraction included information on participants, inclusion and exclusion criteria, intervention details, and outcome measurements. Any disagreements during data extraction were resolved through discussion, and if necessary, a third reviewer was consulted to reach a consensus.

Primary and secondary outcomes

The primary outcomes assessed in this meta-analysis were the frequency of exacerbations of bronchiectasis (BE) and hospitalizations due to these exacerbations. Secondary outcomes included changes in pulmonary function, specifically forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Other secondary outcomes evaluated were sputum scores, levels of cytokines in sputum or bronchoalveolar lavage (BAL) fluid, and the incidence of adverse events, including bacterial resistance.

Bias assessment

The quality of the included studies was independently assessed by two reviewers using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The assessment focused on seven domains: random sequence generation, allocation

concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases. Each domain was rated as having a low, high, or unclear risk of bias. The level of evidence for each outcome was evaluated using the GRADE approach.

Statistical analysis

The final selected RCTs were analyzed using Jamovi 2.4.1 software, specifically the MAJOR section for meta-analysis and Review Manager 5.4 software. Heterogeneity among the RCTs was assessed using the Cochrane Q statistic. After evaluating heterogeneity with the I^2 statistic, a random effects model was applied to account for variability across studies. For dichotomous variables, odds ratios (OR) with 95% confidence intervals (CI) were calculated. For continuous variables, mean differences with 95% CIs were determined. Statistical significance was set at $p<0.05$.

Reporting

The results of this meta-analysis were reported using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Results

We searched 730 articles, of which 4 were eligibile for inclusion to our meta analysis (**Figure 1**).

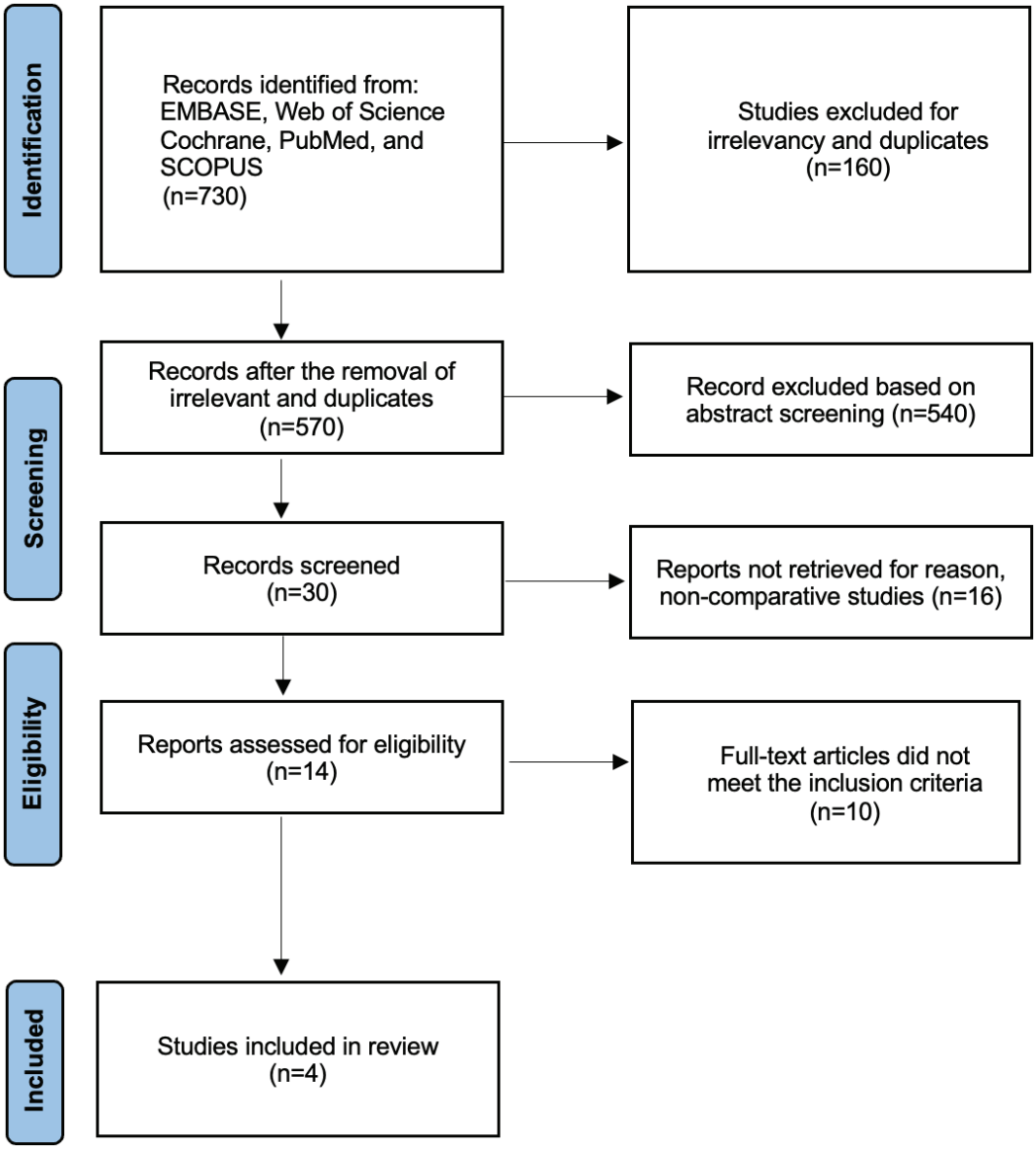

Figure 1: PRISMA flow diagram

A total of 92 patients in Macrolid group and 87 patients in control group were included in this meta analysis. The summarized characteristics of these studies are presented in Table 1. The included RCTs investigated the effects of different macrolides: roxithromycin, erythromycin, azithromycin, and clarithromycin.

Valery et al. administered azithromycin at a dose of 30 mg/kg once a week for up to 24 months, with a placebo group receiving the same regimen for the same duration. Koh et al. evaluated roxithromycin at 4 mg/kg twice a day for 12 weeks, compared to a placebo group for the same period. Yalcin et al. assessed the effects of clarithromycin at 15 mg/kg once daily for 3 months, alongside supportive therapies such as mucolytic and expectorant medications and postural drainage. The control group received only the supportive therapies for 3 months. Finally, Maskela et al. studied erythromycin at a dose of 125 mg (for participants ≤ 15 kg) or 250 mg (for participants > 15 kg) once a day for 52 weeks, compared to a placebo group over the same timeframe (**Table 1**).

Acute exacerbations in bronchiectasis

A total of three study examined the impact of long-term macrolide treatment on the frequency of acute exacerbations in bronchiectasis. Despite variations in macrolide preparations, long-term macrolide use significantly reduced the frequency of acute exacerbations in bronchiectasis (I2=0%) (OR: 0.30, 95% CI: 0.10 to 0.87; p=0.03) (**Figure 2**).

The mean exacerbations of bronchiectasis

Two studies analyzed the mean exacerbations of bronchiectasis per patient. The findings showed that long-term macrolide treatment significantly reduced

Table 1: Summary of the included studies

			Number of patients		Age	
Author	**Year**	**Country**	**Macrolide**	**Control**	**Macrolide**	**Control**
Koh	1997	Korea	13	12	13.3 (2.5)	13 (2.6)
Yalcin	2006	Turkey	17	17	13 (2.7)	12 (2.9)
Valery	2013	Australia	45	44	4 (2.1)	4.2 (2.3)
Masekela	2013	Korea	17	14	8.4 (2.4)	9 (2.1)

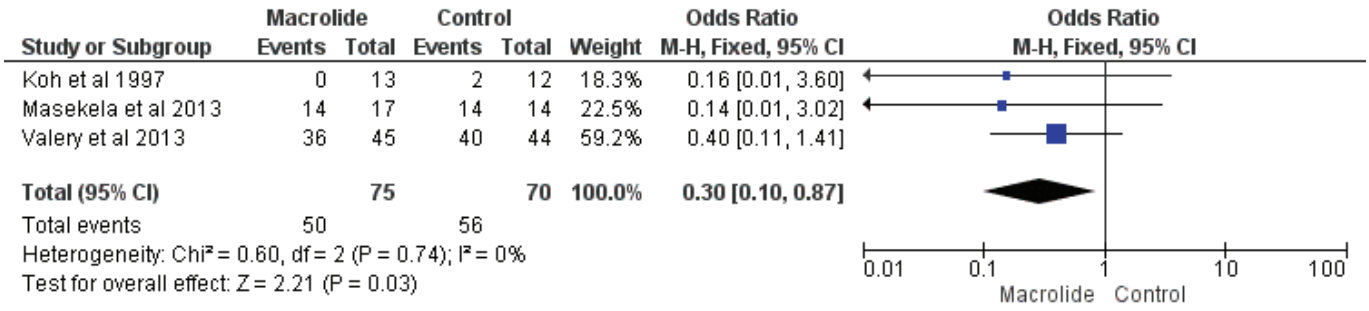

Figure 2: Acute exacerbations in bronchiectasist

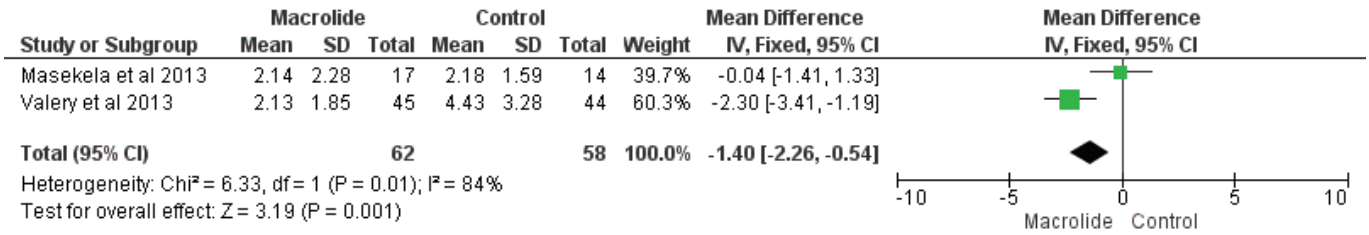

Figure 3: The mean exacerbations of bronchiectasis per patient

the mean exacerbations per patient (I2=84%; WMD -1.40, 95% CI: -2.26 to -0.54; p=0.001) (**Figure 3**).

Frequency of exacerbation-related admissions

One study examined the effect of long-term azithromycin treatment on hospitalization due to exacerbations of bronchiectasis. The results indicated no significant difference in the frequency of exacerbation-related admissions between the azithromycin group and the control group (OR: 0.28, 95% CI: 0.07 to 1.11; p=0.07) (**Figure 4**).

FEV1% predicted at the endpoint

Three studies investigated the effect of long-term macrolide treatment on FEV1% predicted at the endpoint in children with bronchiectasis. The results showed no significant difference in FEV1 between the macrolide treatment group and the control group (I2=80%; WMD 2.21, 95% CI: -2.44 to 6.87; p=0.35) (**Figure 5**).

Changes in FEV1% predicted in patients

Two studies investigated the effect of long-term macrolide treatment on changes in FEV1% predicted in patients with bronchiectasis. The results indicated no significant difference in the changes of FEV1% predicted before and after treatment between the macrolide group and the control group (I2=0%; WMD 2.19, 95% CI: -2.80 to 7.19; p=0.39) (**Figure 6**).

Discussion

This meta-analysis demonstrates that long-term macrolide treatment over 3 to 24 months in pediatric NFBE significantly reduces the frequency of exacerbations, decreasing the mean number of exacerbations per patient during the treatment period. Our analysis provides a comprehensive assessment of the benefits and drawbacks of long-term macrolide treatment specifically for pediatric non-cystic fibrosis BE.

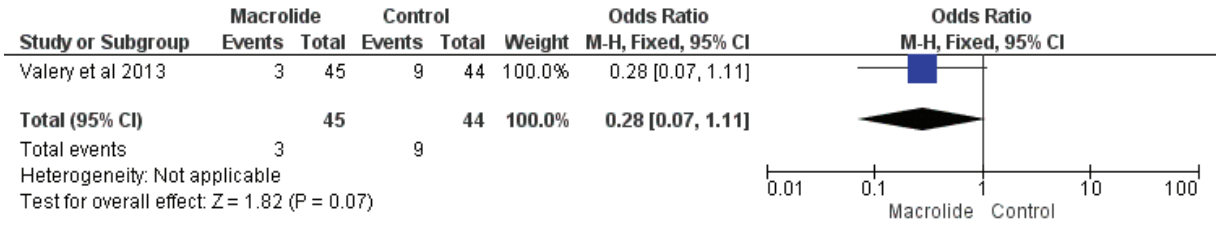

Figure 4: Frequency of exacerbation-related admissions

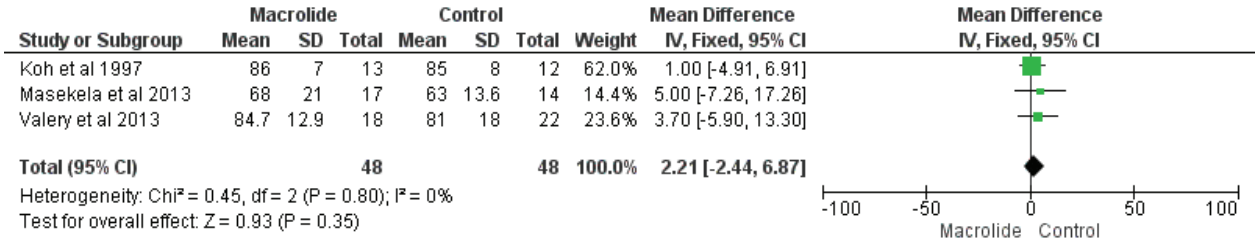

Figure 5: FEV1% predicted at the endpoint

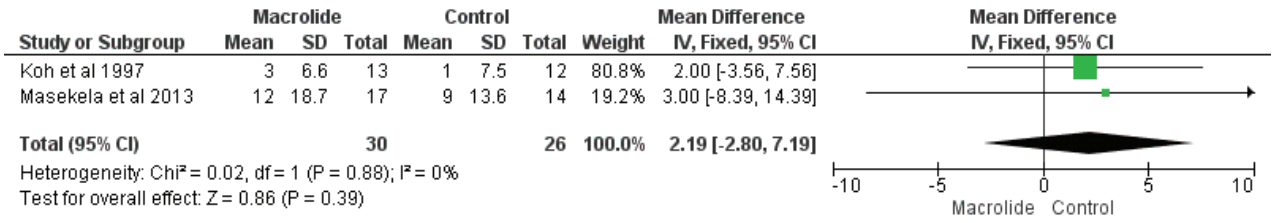

Figure 6: Changes in FEV1% predicted in patients

We analyzed the effects of macrolides on acute exacerbations in pediatric BE using three randomized controlled trials (RCTs). These RCTs involved the administration of roxithromycin for 12 weeks, erythromycin for 52 weeks, and azithromycin for up to 24 months (12-14). Despite differences in study durations and populations, including immunocompromised children due to HIV infection in one RCT, the results consistently showed a reduction in the number of exacerbations.

Although previous research has indicated that a 5-day course of azithromycin can increase the risk of cardiovascular diseases in adults and that long-term macrolide treatment in adults with NCFB can lead to gastrointestinal complications such as diarrhea, nausea, vomiting, and abdominal discomfort, no adverse events were reported in pediatric cases of non-cystic fibrosis BE treated with long-term macrolides compared to the control group (12,16,17). Furthermore, no severe adverse events were reported in children undergoing long-term macrolide treatment for non-cystic fibrosis BE. To mitigate potential risks, future studies should include regular monitoring for complications like cardiovascular diseases. Despite these concerns, long-term macrolide treatment remains a viable option for reducing exacerbations in pediatric non-cystic fibrosis BE.

Limitations

This meta-analysis has several limitations. First, the number of included studies is small, which may limit the generalizability of the findings. Second, variations in study design, macrolide preparations, and treatment durations could introduce heterogeneity. Third, the inclusion of different pediatric populations, including immunocompromised children, may affect the consistency of the results. Additionally, the potential for publication bias and the lack of long-term follow-up data on adverse effects and antibiotic resistance are concerns. Further large-scale, long-term studies are needed to confirm the efficacy and safety of macrolide treatment in pediatric non-cystic fibrosis bronchiectasis.

Conclusions

This meta-analysis reveals that long-term macrolide treatment, spanning 3 to 24 months, significantly reduces the frequency of exacerbations in pediatric NCFB. Despite variations in study durations and macrolide preparations, the consistent reduction in exacerbation frequency highlights the effectiveness of macrolides in managing NCFB. However, the treatment did not significantly impact FEV1% predicted or hospitalization rates due to exacerbations. These findings underscore the potential benefits of long-term macrolide therapy in reducing exacerbations, though further research is needed to fully understand its impact on pulmonary function and hospitalization rates in pediatric NCFB.

Conflict of interest: The authors report no conflict of interest.

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Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors. No need for meta-analysis.

Informed consent: No need for meta-analysis.

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Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contributions

Research concept and design: RDG, MAU, MAA, ARY

Data analysis and interpretation: RDG, MAA, ARY, HM, IA

Collection and/or assembly of data: RDG, MAU, MAA, ARY, HM, IA

Writing the article: MAA, ARY, HM, IA

Critical revision of the article: RDG, MAU, HM, IA

Final approval of the article: RDG, MAU, MAA, ARY, HM, IA

All authors read and approved the final version of the manuscript.

References

1. Ramsey KA, Schultz A. Monitoring disease progression in childhood bronchiectasis. Front Pediatr. 2022;10:1010016.
2. Gallucci M, Candela E, Di Palmo E, Miniaci A, Pession A. Non-Cystic Fibrosis Bronchiectasis in Pediatric Age: A Case Series in a Metropolitan Area of Northern Italy. Children (Basel). 2022;9(9):1420.
3. Lee E, Shim JY, Kim HY, Suh DI, Choi YJ, Han MY et al. Clinical characteristics and etiologies of bronchiectasis in Korean children: A multicenter retrospective study. Respir Med. 2019;150:8-14.
4. Guan Y, Zhang X, Yang H, Xu H, Zhao S. Long-Term Azithromycin Treatment in Pediatric Primary Ciliary Dyskinesia: A Retrospective Study. Front Pediatr. 2022;10:905253.
5. Wolter J, Seeney S, Bell S, Bowler S, Masel P, McCormack J. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. Thorax. 2002;57(3):212-6.
6. Lee E, Lee YY. Risk factors for the development of post-infectious bronchiolitis obliterans after Mycoplasma pneumoniae pneumonia in the era of increasing macrolide resistance. Respir Med. 2020;175:106209.
7. Emiralioğlu N, Öztürk Z, Yalçın E, Doğru D, Özçelik U, Kiper N. Long term azithromycin therapy in patients with cystic fibrosis. Turk J Pediatr. 2016;58(1):34-40.
8. Wang D, Fu W, Dai J. Meta-analysis of macrolide maintenance therapy for prevention of disease exacerbations in patients with noncystic fibrosis bronchiectasis. Medicine (Baltimore). 2019;98(17):e15285.
9. Gao YH, Guan WJ, Xu G, Tang Y, Gao Y, Lin ZY, et al. Macrolide therapy in adults and children with non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. PLoS One. 2014;9(3):e90047.
10. Kelly C, Chalmers JD, Crossingham I, Relph N, Felix LM, Evans DJ, et al. Macrolide antibiotics for bronchiectasis. Cochrane Database Syst Rev. 2018;3(3):CD012406.
11. Khan J, Moran B, McCarthy C, Butler MW, Franciosi AN. Management of comorbidities in difficult and severe asthma. Breathe (Sheff). 2023;19(3):230133.
12. Koh YY, Lee MH, Sun YH, Sung KW, Chae JH. Effect of roxithromycin on airway responsiveness in children with bronchiectasis: A double-blind, placebo-controlled study. Eur Respir J. 1997;10:994-9.
13. Masekela R, Anderson R, Gongxeka H, Steel HC, Becker PJ, Green RJ. Lack of efficacy of an immunomodulatory macrolide in childhood HIV related bronchiectasis: A randomised, placebo-controlled trial. J Antivir Antiretrovir. 2013;5:044–49.
14. Valery PC, Morris PS, Byrnes CA, Grimwood K, Torzillo PJ, Bauert PA, et al. Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): A multicentre, double-blind, randomised controlled trial. Lancet Respir Med. 2013;1:610–620.
15. Yalcin E, Kiper N, Ozcelik U, Dogru D, Firat P, Sahin A, et al. Effects of claritromycin on inflammatory parameters and clinical conditions in children with bronchiectasis. J Clin Pharm Ther. 2006;31:49–55.
16. Wu Y, Bi WT, Qu LP, Fan J, Kong XJ, Ji CC, et al. Administration of macrolide antibiotics increases cardiovascular risk. Front Cardiovasc Med. 2023;10:1117254.
17. Dhar R, Talwar D, Singh V, Dumra H, Rajan S, Jindal SK. Expert recommendations on the role of macrolides in chronic respiratory diseases. Lung India. 2021;38(2):174-82.