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SYSTEMATIC REVIEW

Efficacy of Macrolides on Acute Asthma or Wheezing Exacerbations in Children with Recurrent Wheezing: A Systematic Review and Meta-analysis

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Abstract

Introduction The role of macrolides for treatment of children with acute asthma or wheezing exacerbations is unclear.

Objective The aim of this systematic review was to evaluate the effectiveness of macrolides in children with recurrent wheezing presenting with acute asthma or wheezing exacerbation.

Methods We conducted an electronic search in MEDLINE, EMBASE, CINAHL, LILACS, CENTRAL, and ClinicalTrials.gov.

Study selection criteria Randomized controlled trials of macrolides (any macrolide) compared with placebo or standard treatment in children up to 18 years with recurrent wheezing/asthma presenting with an acute exacerbation.

Outcomes Primary outcomes were need for hospitalization and/or time of acute asthma/wheezing symptoms resolution; secondary outcomes were duration of stay in the emergency department (ED)/clinic, severity of symptoms of the index episode, use of additional systemic corticosteroids or short active β-2 agonists, changes in lung function measures, ED visit/hospitalization during first week after index episode, time to next exacerbation, or adverse effects (AEs).

Results Only three studies met the inclusion criteria ($n = 334$ children, 410 treated episodes); two studies included recurrent wheezers and the third included asthmatic children. There was no difference in hospitalization between groups, but children treated with macrolides had a significantly lower time to symptoms resolution than controls, although the magnitude of benefit remains to be quantified due to no normal distribution data presented. There was no difference in time to next episode of exacerbation (HR 0.96; 95% CI 0.71–1.28; $I^2 = 0\%$; $p = 0.77$). In one study, children receiving macrolides had a significant decrease in the severity of symptoms, decrease use of salbutamol, and another study showed improved lung function. No study evaluated antibiotic resistance development.

Conclusions Limited evidence support that a macrolide trial could be considered in children with acute asthma or recurrent wheezing exacerbation.

1 Introduction

Asthma is one of the most common chronic, non-communicable diseases, and affects around 334 million people worldwide [1, 2]. Asthma affects people from all age groups and presents its peak incidence in childhood. Recent data from the general population showed that in children up to 5 years old, and for those aged between 12–17 years, the overall asthma incidence rates were 23/1000 and 4.4/1000 children per year, respectively [3]. Asthma affects quality of life, productivity at work and school, healthcare use, and can result in death. Asthma also places a significant economic burden on health systems; for example, in the US the total cost of asthma was estimated to be US$81.9 billion in 2013 [4]. Is important to mention that 48% of preschoolers with asthma had an exacerbation in the preceding year [5]. The

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Key Points

Asthma in children is a heterogeneous disease and the best treatment for asthma exacerbations is still under debate, especially in younger children.

Macrolides, due to their immunomodulatory and anti-inflammatory capacities, have been progressively studied and it has been hypothesized that macrolides may be helpful in asthma or wheezing exacerbations.

We found limited evidence that macrolides reduce symptoms and duration of asthma exacerbation episodes and could be considered in children with recurrent wheeze.

More studies need to be done to identify the group of children that can respond better to macrolides treatment and to measure the real risk of macrolide resistance development.

annual rate of emergency department (ED) visits was 23–42 per 1000 for preschoolers and < 15 per 1000 for those aged 6–70 years, with the same pattern for hospitalizations [6, 7]. Furthermore, the age at first hospitalization for asthma has decreased over time [8]. Thus, the economic burden of poor asthma control in preschoolers is of paramount importance [9].

Two meta-analyses have confirmed the beneficial role of inhaled corticosteroids (ICS) among preschoolers with asthma or recurrent wheezing exacerbation, with daily medium-dose ICS reducing the risk of exacerbations by up to 40% [10, 11]. Even though international guidelines for treating acute asthma or recurrent wheezing exacerbations in preschoolers and school children recommend the use of systemic corticosteroids (SCS) for episodes that do not respond to short-acting β-2 agonists (SABA), recent studies have questioned the utility of this intervention in preschoolers [12, 13].

Therefore, additional approaches to prevent exacerbations have recently been investigated. Macrolides have beneficial anti-inflammatory effects in other inflammatory chronic lung diseases [14], and may also provide benefits in children with episodic wheeze based on their effect on the airway microbiome, as accumulating evidence suggests that bacteria are important determinants of asthma inception and progression [15]. Macrolides are already one of the most prescribed antibiotics in ED in the US; a recent study showed that macrolides were prescribed in 17% (1.1 million) of all visits to EDs in which antibiotics were prescribed, and the most frequently diagnoses where macrolides were used included acute otitis media (17%), non-viral pneumonia (14%), pharyngitis or tonsillitis (12%), bronchitis or bronchiolitis (11%;), and upper respiratory tract infection (10%) [16].

In consideration of the controversy in the treatment of acute asthma exacerbations, especially in preschoolers with recurrent wheezing without persistent symptoms; the progressive evidence of the mechanisms of action of macrolides; and the widespread use of macrolides in children, we decided to perform this systematic review to evaluate the efficacy of macrolides in episodes of acute asthma or wheezing exacerbations in childhood.

2 Methods

2.1 Search and Selection Criteria

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO, http://www.crd.york.ac.uk/PROSPERO) as CRD42018115926. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to perform this review [17]. The authors identified studies published in MEDLINE—PubMed, EMBASE—Elsevier, LILACS—BIREME, the Cochrane Controlled Trials Register (CENTRAL) CINAHL—EBSCO databases, and ClinicalTrials.gov until September 2019, using the terms 'asthma', 'acute asthma', 'asthma attack', 'asthma exacerbation', 'wheezing', 'wheeze', 'recurrent wheezer', 'recurrent wheeze', 'acute wheeze', 'wheezing episode', 'asthma episode', 'lung symptoms', 'macrolides' 'azithromycin', 'clarithromycin', 'erythromycin' and 'telithromycin'; we used free text, MeSH terms, Boolean operators and randomized controlled trial (RCT)/age limitations (filters) in different combinations (search details in supplement). Additionally, a search of relevant files from the drug manufacturer's databases (published and unpublished) was performed. Language restrictions were not applied. To be included, studies had to meet all the following criteria: (i) children (preschoolers to adolescents aged up to 18 years) with recurrent wheezing/asthma presenting with an acute exacerbation; (ii) RCTs (parallel group or cross-over design) of any duration; (iii) comparison of macrolide (any type) with placebo or standard care, only when standard care did not include an antibiotic; and (iv) report at least one of the following primary outcomes: need for hospitalization and/or time to acute asthma/wheezing symptoms resolution; or the following secondary outcomes: duration of staying in the ED/clinic, severity of symptoms of the index episode, use of additional SCS or SABA, changes in lung function measures, ED visit/hospitalization during first week after index episode, time to next exacerbation, macrolides resistance or adverse effect (AEs) or severe adverse events (SAEs) of macrolides. An SAE was defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability or incapacity [18].

We excluded studies that exclusively involved patients with their first wheezing episode or bronchiolitis episode and other chronic respiratory conditions (e.g., bronchopulmonary dysplasia, cystic fibrosis, primary ciliary dyskinesia, post-infection bronchiolitis obliterans) or congenital cardiopulmonary conditions. We also excluded studies that involved use of macrolides for asthma chronic treatment or long-term use.

2.2 Data Extraction and Assessment of Risk of Bias

Titles, abstracts, and citations were independently analyzed by two of the authors (JCR and MP). From the full text, all studies were independently assessed for inclusion. Both authors were independently involved in all stages of study selection, data extraction, and risk of bias assessment. The latter was assessed according to recommendations outlined in the Cochrane Handbook [19] for the following items: (i) adequacy of sequence generation; (ii) allocation concealment; (iii) blinding of participants and investigators; (iv) blinding of outcome assessment; (v) incomplete outcome data; (vi) selective outcome reporting and other bias. Disagreements were discussed and resolved by the third investigator (LBB).

2.3 Data Analysis

Analysis was performed by intention to treat and included all participants to minimize bias.

Outcomes were pooled using mean differences (MD) (inverse variance method) or Mantel–Haenszel risk ratios (RR). Estimate precision was quantified by 95% confidence intervals (CI). Statistical heterogeneity was measured by the I^2 test ($\leq 25\%$ low heterogeneity; 26–39% unimportant; 40–60% moderate; and 60–100% substantial heterogeneity) [20]. A fixed-effects model was used when there was no evidence of significant heterogeneity in the analysis ($I^2 < 40\%$); if significant heterogeneity was found, a random-effects model was used [21, 22]. We presumed that the clinical heterogeneity between studies should be low, especially considering the narrow inclusion criteria. If clinical heterogeneity appeared to be high, we used a random-effects model. *A priori* subgroup analyses included type of macrolides, age (< 5 years versus > 5 years), severity of exacerbation (mild vs moderate to severe), atopic versus non-atopic children, and trials sponsored by pharmaceutical industry versus independent trials. The meta-analysis was performed with the Review Manager 5.3.5 software (Cochrane IMS, 2014).

3 Results

A total of 814 studies were found in a preliminary search; 787 were included from the databases search and 27 studies were included from the cross-reference search. Of these, seven studies were left after duplicates were removed and title and abstract were reviewed. We performed a full-text review of the seven articles; four of these studies were excluded because one did not have a comparison group [23], one had insufficient clinical data [24], one used macrolide intervention prior to lower respiratory tract symptoms [25], and one was an ongoing study (NCT02003911) (Fig. 1).

3.1 Included Studies

Three studies [26–28] published between 2012 and 2017 met our selection criteria and were included for quantitative analysis. These studies included 334 patients (aged 12 months to 14 years, 40–70% males; two studies [27, 28] recruited preschoolers and in the other study [26] the mean age was 9.09 ± 2.67 years) who presented a total of 410 episodes of acute asthma or lower respiratory symptoms. One study was performed in Canada [28], one in Greece [26], and one in Denmark [27]. We contacted the authors of two studies [26, 27] for additional data or clarifications. A summary of the characteristics of included studies is presented in Table 1.

As in our protocol, all included studies were randomized parallel-group trials. Two studies [27, 28] were blinded and one [26] was an open study. In two studies [26, 28], the randomization was done for each patient, and one study [27] randomized each episode of exacerbation (the number of episodes randomized per patient was 2.2 ± 1.5). One study [28] recruited patients presenting at the ED with wheezing, one study [26] recruited patients from a pediatric clinic, and one [27] study included patients from the $COPSAC_{2010}$ birth cohort. This cohort is a single-center, population-based birth cohort of 700 children recruited from Danish population at 1 week of age and followed up prospectively at the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) research unit.

All included patients met the criteria of acute asthma episodes, but with variation in the definition and severity. Mandhane et al. [28] included patients aged 12–60 months who presented in ED with a wheeze episode confirmed by physician or nurse; 62% were diagnosed with allergy or atopy, 35% were treated with ICS, 88% had previously had at least one episode of wheeze, and 35–40% had ever been diagnosed with asthma. This study included patients with a first episode of wheezing (29% of the sample) but presented data excluding this group of patients. Therefore, we considered

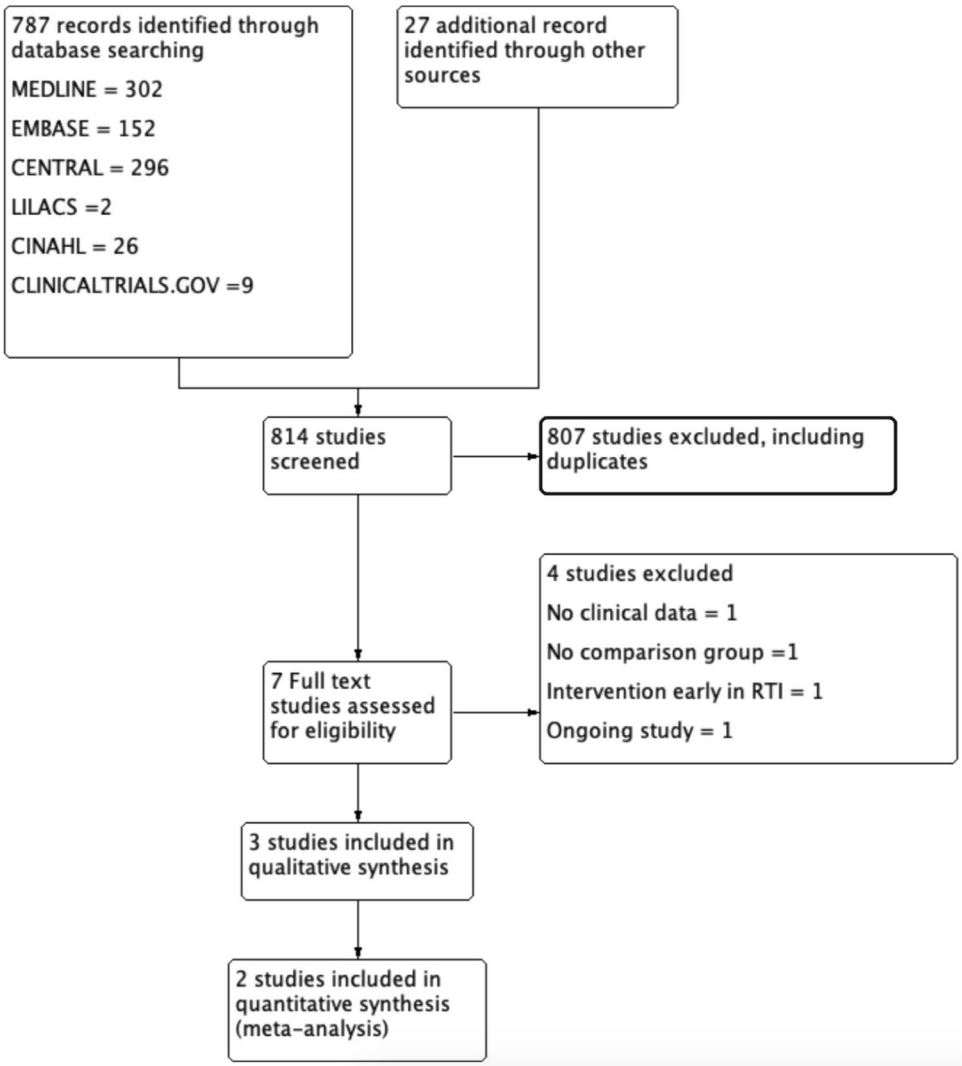

Fig. 1 Process of study selection. *CENTRAL* cochrane central register of controlled trials, *CINAHL* cumulative index to nursing and allied health literature, *LILACS* Latin American and Caribbean Literature on Health Sciences, *RTI* respiratory tract infection

only data from children with previous wheezing history in the outcomes and subgroup analysis whenever available. Koutsoubari et al. [26] included patients (6–14 years of age) diagnosed with intermittent or mild persistent asthma according to GINA (Global Initiative for Asthma) guidelines; 50% were atopic, 60% received ICS, and 4–22% were admitted for asthma exacerbation before the study. Stokholm et al. [27] included patients (1–3 years of age) diagnosed with recurrent asthma-like symptoms (troublesome symptoms consisting of cough, wheeze, or dyspnea, with a frequency of five episodes within 6 months or 4 weeks of continuous symptoms or a severe acute episode needing oral corticosteroids [OCS] or hospital admission) lasting at least 3 days. Almost 30% of the sample had atopic dermatitis, 11–15% had sensitization (skin prick test or specific IgE), and 28–44% had history of maternal asthma. Patients recieved concurrent ICS in 82% and montelukast in 60% of the randomized episodes.

Only one study [28] excluded patients who had previously received antibiotic therapy. Interestingly, in that study 69% of preliminary eligible children were excluded because they had received antibiotics within the prior 30 days. The presence of viral or bacterial infections was evaluated in two studies [26, 27]. Stokholm et al. [27] found a pathogenic bacteria in 90 of 135 tested episodes (67%), the most common bacteria identified was *Moraxella catarrhalis*, and any pathogenic virus was found in 58 of 135 tested episodes (43%) with similar distribution between rhinovirus, respiratory syncytial virus (RSV), and enteroviruses. Koutsoubari et al. [26] found that nasal washes were positive in 26/40 (65%) patients, (18 rhinovirus, 3 adenovirus, 2 *Mycoplasma pneumoniae*, 2 parainfluenza, 1 RSV, no *Chlamydophila pneumoniae*) and there were two patients with serologically confirmed mycoplasma infection, one in each group ($p = 0.704$). All studies used macrolides for intervention in acute presentation but with different starting criteria and settings. Mandhane et al. [28] started the intervention in patients presenting in ED with wheeze exacerbation, Koutsoubari et al. [26] started the intervention in patients with

Table 1 Characteristics of included studies

Study	Design	Place	Patients *n* (% male)	Randomized subject	Macrolides mean age (year) (SD)	Placebo mean age (year) (SD)	Treated episodes	Intervention	Comparison	Setting of intervention	Treatment prior to randomization	% Asthma diagnosed by physician	Reported outcomes
Koutsoubari et al. [26] 2012	R, O, PG	Greece	40 (45)	Patients	9.1 (2.67)	8.4 (2.47)	40	Clarithromycin 15 mg/kg daily for 3 weeks	Standard care	Clinic	Clarithromycin: ICS 61.1% Control: ICS 59.1%	100%	Days without symptoms after inclusion Number and severity of periods with loss of control Time to loss of control Duration and severity of the index exacerbation Peak flow rate variability and lung function
Stokholm et al. [27] 2016	R, DB, PG	Denmark	72 (65)	Events	2.0 (0.6)	2.0 (0.6)	148	Azithromycin 10 mg/kg once daily for 3 days	Placebo	Clinic	Azithromycin: ICS 82% Montelukast 60% Placebo: ICS 80% Montelukast 57%	NR	Duration of episodes after initiation of treatment Time from treatment to the next episode Number of episodes that turned into severe exacerbations (admission or use of oral steroids) Duration of β2 agonist use after treatment Adverse events
Mandhane et al. [28] 2017	R, DB, PG	Canada	222 (72.1) Prior wheeze = 158[a]	Patients	2.9 (1.13)	2.54 (1.16)	222	Azithromycin 10 mg/kg for 1 day and 5 mg/kg/day for 4 days	Placebo	ED	Azithromycin ICS 35.5% Montelukast 5.5% Placebo: ICS 36.6% Montelukast 4.5%	Azithromycin 50.6% Placebo 44.3%	Time to symptom resolution SABA use Time to exacerbation

R randomized, *O* open, *PG* parallel group, *DB* double blind, *y* years, *SD* standard deviation, *ED* emergency department, *ICS* inhaled corticosteroids, *NR* not reported, *SABA* Short-acting β2 agonist

[a]Number of included patients with prior wheezing episodes

asthma exacerbation suspected by parents and confirmed by study physician, and in Stokholm et al. [28], the study intervention was started in patients who presented an episode defined as three consecutive days of troublesome lung symptoms (only 18% of the included patients had confirmed objective wheezing).

Azithromycin was the most used intervention [27, 28]; only one study [26] used clarithromycin. Details of specific doses used and days of treatment are listed in Table 1. Two studies [27, 28] compared intervention with matching placebo. Koutsoubari et al. [26] compared intervention with standard care (oxygen, SABA, anticholinergics, and SCS according to clinical judgment). The three included studies [26–28] used SABA as needed. Montelukast and ICS were also used in some of the studies but not per protocol. Two [27, 28] reported funding information and all were funded by an independent sponsor. No pharmaceutical company funded any of the studies (Table 1).

3.1.1 Risk of Bias of Included Studies

We included three studies, all of which were properly randomized by computer, although one was limited by its open design. We judged unclear risk of bias in two studies because of the lack of a prospective register and apparently incomplete reported outcomes, although it appears not to be a source of high risk of bias. Risk of bias judgement of included studies is summarized in Fig. 2 and detailed in Table 2.

3.2 Primary Outcomes

3.2.1 Hospitalization

Two studies [26, 27] reported data for hospitalization outcome in established acute episodes confirmed by a physician. Stokholm et al. [27] presented mixed data on admission to hospital and the need for oral corticosteroids in the randomized episodes (three in the azithromycin group and two episodes in the placebo group). Koutsoubari et al. [26] reported that none of the included patients required hospitalization during the study period.

3.2.2 Time to Resolution of the Episodes

All studies [26–28] reported this outcome in a non-normal distribution of the data, so we were unable to perform a meta-analysis. Two studies [26, 27] showed a statistically significant reduction in the time for episode resolution, using macrolides versus placebo [27] or versus standard care [26]. Stokholm et al. [27] reported that the average number of symptom days was 3.4 in the azithromycin group versus 7.7 days in the placebo group, with a reduction in episode length in 63.3% (95% CI 56.0–69.3; $p < 0.0001$). Restricted to the first randomized episode, the mean duration was 4.0 days for the azithromycin group and 7.1 days for the placebo group with a reduction in symptom duration of 44% (95% CI 30.9–55.2; $p < 0.0001$). The reduction effect was better if the treatment was initiated before day 6 of the episode than if initiated ≥6 days after the episode (83% vs 36%; $p < 0.0001$). Concurrent treatment with ICS or montelukast did not significantly modify the treatment effect (p value for interaction = 0.57 for ICS, and $p = 0.69$ for montelukast). Similarly, Koutsoubari et al. [26] found a significantly shorter index episode median with clarithromycin compared with the control group, (5 [IQR 1] vs 7.5 [IQR 1], respectively; $p < 0.00001$); also, a significant reduction in the total duration of periods of loss of control was reported with clarithromycin versus controls (median 0.5 [IQR 3] vs 7 [IQR 5] for control group; $p < 0.00001$). The total duration of the loss of control episodes was 7.9 fewer days compared with control, independent of steroid administration. In the third study [28], a similar median time for resolution of symptoms was reported between azithromycin and placebo groups (4 days [IQR 3–7] and 4 days [IQR 3–6]; $p = 0.49$, respectively).

Only Stokholm et al. [27] reported data by atopic condition in this outcome and found that differences in episode duration were unrelated to allergic sensitization to inhalant or food allergens at 6 or 18 months of age ($p = 0.173$), or to atopic dermatitis presence ($p = 0.323$). No data was available to perform any planned subgroup analysis for this outcome.

As additional information, two studies [26, 27] reported time to resolution related to microbiological status. In one study [27], the presence of any pathogenic bacteria or virus during the episodes did not significantly modify the treatment effect, with the exception of *Haemophilus influenzae,* where azithromycin was more effective than placebo (2.7 vs 12.1 days, 77% reduction time [95% CI 58–87.4]; $p \leq 0.0001$). In the other study [26], the presence of rhinovirus did not affect any of the outcomes in either groups; and since the presence of confirmed *Mycoplasma pneumoniae* was very low, no analysis could performed.

3.3 Secondary Outcomes

3.3.1 Time to Next Exacerbation

All studies [26–28] reported data for the next asthma or asthma-like exacerbation. We pooled the data from the two studies [27, 28] that reported hazard ratios (HRs) for the second episode of exacerbation or loss of control of symptoms and found no significant difference between preschoolers receiving macrolides versus placebo, HR 0.96 (95% CI 0.71–1.28; $I^2 = 0\%$, $p = 0.77$) (Fig. 3). However, Koutsoubari et al. [26] described that the time to first period of loss of

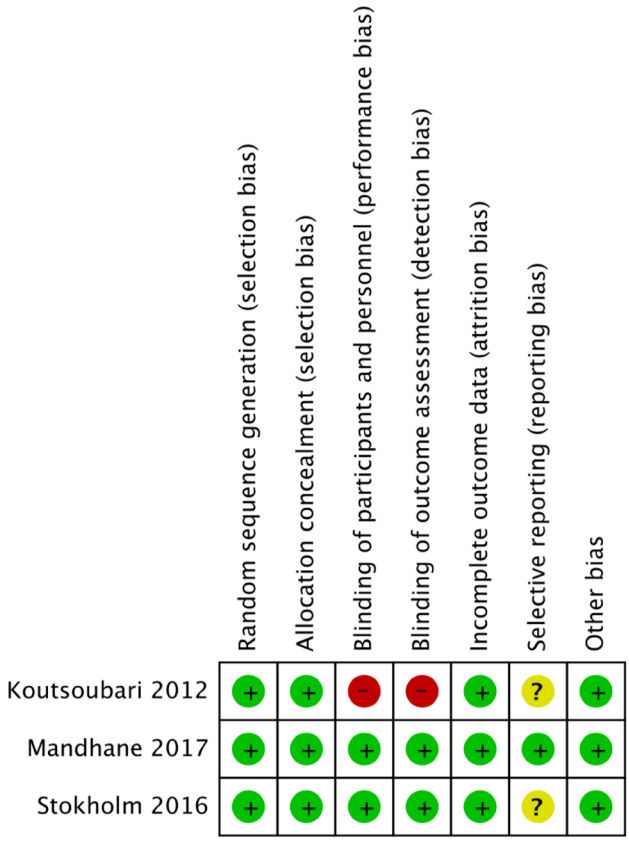

Fig. 2 Risk of bias of the eligible studies

control was significantly prolonged in the macrolide group compared with the control group (67.5 days [IQR 38] vs 26.5 days [IQR 33]; $p = 0.003$). This study found no difference between atopic and non-atopic patients. Not enough data were available to perform the sub-analysis by atopy or age group in this outcome.

3.3.2 Severity of Symptoms

Only one study [26] reported this outcome. The severity according to diary score was lower in the clarithromycin group than the control group during the index episode (14 [IQR 3] vs 18 [IQR 2]; $p = 0.0002$). There were no differences noted in this outcome between atopic and non-atopic children.

3.3.3 Short-Acting β-2 Agonists (SABA) Use

Two studies [27, 28] of preschoolers reported this outcome. However, these studies reported these data in different units, precluding the possibility of performing a meta-analysis. Mandhane et al. [28] described no significant difference in the number of days using SABA between azithromycin and placebo groups (5 days [IQR 1.3–7] vs 6 days [IQR 3–10]; $p = 0.10$, respectively). However, Stokholm et al. [27] reported that treatment with azithromycin reduced the duration of treatment with SABA after intervention: 8.9 days for azithromycin versus 10.1 days for placebo group, a 22.0% reduction (95% CI 7.0–34.6; $p = 0.006$). No data were available to perform the sub-analysis by atopy condition for this outcome.

3.3.4 Lung Function

Only one study [26] reported lung function data. There was a significant difference in minimum morning peak expiratory flow (PEF) during index asthma exacerbation between clarithromycin and control group (214.7 ± 49.1 L/min vs 275 ± 83.7 L/min, $p = 0.032$).

No significant difference between atopic and non-atopic subjects was found for this outcome. No data were available to perform the sub-analysis by age group in this study.

3.3.5 Use of Additional Systemic Corticosteroids (SCS)

Only one study include information for use of SCS as a measured outcome; Stokholm et al. [27] reported mixed data of admission to hospital and need for oral corticosteroids in the randomized episodes (three episodes in the azithromycin group and two episodes in the placebo group).

3.3.6 Adverse Events

Two studies [27, 28] reported this outcome; however, we excluded the Mandhane et al. [28] study because data for this outcome were not reported exclusively for recurrent wheezers. The most common AE described was gastrointestinal effects. Stokholm et al. [27] reported two SAEs, one hospitalization for gastroenteritis 4 days after RCT randomization in the azithromycin group and one hospitalization for pneumonia 20 days after randomization in the placebo group ($p = 0.99$) [29]. No other SAEs were reported in the rest of the studies.

3.3.7 Other Outcomes

We did not find any study that reported data for the following outcomes: antibiotics resistance, duration of staying in the ED/clinic, or ED visit during the first week after index episode.

4 Discussion

To our knowledge, this is the first systematic review of macrolides use exclusively in children with acute asthma or recurrent wheezing exacerbations. Two out of three [27, 28]

Table 2 Risk of bias of the eligible studies

Bias	Authors' judgement	Support for judgement
Koutsoubari et al. 2012 [26]		
Random sequence generation (selection bias)	Low risk	"A computerized randomization table, blinded to patients and to the study physician, was used to allocate children"
Allocation concealment (selection bias)	Low risk	"A computerized randomization table, blinded to patients and to the study physician, was used to allocate children"
Blinding of participants and personnel (performance bias)	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Open-label study
Incomplete outcome data (attrition bias)	Low risk	"No patient/parent dropped out of the study after randomization"
Selective reporting	Unclear risk	Not prospective registration, all outcomes described in methods were reported
Other bias	Low risk	No other significant source of bias identified
Stokholm et al. 2016 [27]		
Random sequence generation (selection bias)	Low risk	"Treatments were randomly allocated at the Pharmacy of Glostrup (Copenhagen, Denmark) with a computer-generated list of random numbers in blocks of ten"
Allocation concealment (selection bias)	Low risk	"Copies of the randomization code were kept in sealed envelopes at the research site and the pharmacy" "Investigators and participating families were masked to treatment assignment"
Blinding of participants and personnel (performance bias)	Low risk	"Investigators and participating families were masked to treatment assignment"
Blinding of outcome assessment (detection bias)	Low risk	"Those assessing the primary outcome were masked; those doing subanalyses were not"
Incomplete outcome data (attrition bias)	Low risk	Excluded patients were properly described
Selective reporting	Unclear risk	Prospective registration, almost every registered outcome was reported
Other bias	Low risk	No other significant source of bias identified
Mandhane et al. 2017 [28]		
Random sequence generation (selection bias)	Low risk	"The Drug Development and Innovation Center generated the random allocation sequence using random-number generating software"
Allocation concealment (selection bias)	Low risk	"The allocation sequence was concealed from research assistants, investigators and participants"
Blinding of participants and personnel (performance bias)	Low risk	All investigators, research assistants, and participants were masked to allocation of treatment
Blinding of outcome assessment (detection bias)	Low risk	All investigators, research assistants, and participants were masked to allocation of treatment. Participants, study personnel, study investigators, and data analysts were blinded to allocation group
Incomplete outcome data (attrition bias)	Low risk	Clearly reported excluded patients with incomplete data
Selective reporting	Low risk	Prospective registration, all outcomes were reported
Other bias	Low risk	No other significant source of bias identified

studies included had an overall low risk of bias. We found that in two of the studies, children treated with macrolides had a significantly shorter time to symptom resolution than controls; and among secondary outcomes, children receiving macrolides had a significant decrease in the severity of symptoms, decreased use of SABA, and improved lung function (PEF) compared with controls. However, the magnitude of these benefits remains to be quantified because it was not possible to perform a meta-analysis. In contrast, no differences in reducing either hospitalization or time to the next exacerbation were found using macrolides or placebo.

Diagnosis of asthma in preschoolers is challenging. Further, the overlapping clinical presentation of viral infection-induced wheezing episodes, bronchiolitis, lower respiratory tract infection (LRTI), and asthma exacerbations is subtler among younger children. In the present review, two out of

three studies [27, 28] included preschoolers with a minimum age limit of nearly 24 months; almost all of these included patients had experienced at least three episodes of acute exacerbation episodes ('recurrent wheezers'), and 27–53% had history of parental asthma; one [28] of these studies also included data from children with bronchiolitis, but only data on preschoolers with recurrent wheeze were used in our analysis. The other study [26] included school children diagnosed with intermittent or mild persistent asthma according GINA guidelines.

A recent Cochrane review [30] evaluated the use of antibiotics in acute asthma exacerbation including three studies in children, only one of them used macrolides [26] and was included in our review. The authors found limited evidence that antibiotics given at the time of an asthma exacerbation may lead to more symptom-free days at follow-up and improved PEFR at 10 days compared with standard care or placebo, but with low confidence in the effect estimates [30]. Another systematic review [31] included RCTs in children with 'reactive airway diseases' (asthma, recurrent wheezing, and bronchiolitis) where macrolides were used for chronic and acute exacerbation treatment. They found that macrolides significantly improve lung function, lessen SABA use and recurrent wheezing, and limit growth of *Moraxella catarrhalis* from nasal swabs. Also, the same group of authors recently published a systematic review [32] of macrolides used exclusively during hospitalization of children with 'reactive airway disease' (asthma, recurrent wheezing and bronchiolitis) in which they found no effect on length of stay, oxygen duration, distress, and re-admission rates. However, the focus of these three systematic reviews [30–32] are completely different than in our review, where only RCTs of macrolides in children with recurrent wheezing presenting with acute asthma or wheezing exacerbation were included.

In our review of three pediatric studies, we found that there were no significant differences in RR of hospitalization between macrolides and controls. However, for the other primary outcome, in two [26, 27] out of three studies, children on macrolides had significantly shorter times to resolution than those in the control group . Considering only data from preschoolers, one study [27] showed a significant reduction in time to symptom resolution of 44% with macrolides versus controls, but the other study [28] showed no difference between medians for this outcome. Among our secondary outcomes, only one [27] out of two [27, 28] studies showed a significant reduction in number of treated days with SABA. In relation to symptoms and progression to severe events, the use of macrolides significantly reduces the severity of symptoms of the index episode in the only study [26] that reported this outcome. Only one study [26] reported lung function, with significant improvement in PEF using macrolides compared with placebo. There was no difference in the outcomes between atopic or non-atopic patients, sensitized patients, or in patients with a family history of asthma [27].

Four studies were excluded in our review: Fonseca-Aten et al. [24], Volovitz et al. [23], Bacharier et al. [25], and an ongoing study (ClinicalTrials.gov identifier NCT02003911). Briefly, Fonseca-Aten et al. [24] conducted a randomized, placebo-controlled study enrolling 43 patients (4–17 years of age) that consulted in the ED with an acute exacerbation of wheezing. The intervention was clarithromycin 15 mg/kg twice daily for 5 days, and the primary outcome was total cytokine concentrations. Patients using clarithromycin had significantly and persistently lower nasopharyngeal concentrations of TNF-α, IL-1β, and IL-10 in children treated with clarithromycin compared with placebo, highlighting one of the proposed non-antibiotic mechanisms of action of macrolides. However, insufficient clinical data was reported to be included in our systematic review. Volovitz et al. [23], in a quasi-randomized crossover study including 100 children (5 months to 5 years old) with recurrent asthma exacerbations, included three protocols of treatment, one of which used azithromycin without any control group. Therefore, we decided not to include this study in our systematic review. Bacharier et al. [25] enrolled 607 participants and examined azitromycin intervention versus placebo prior to lower respiratory tract symptoms. This intervention was used at home by parents in respiratory tract infection (RTI) episodes as soon as included participants developed the symptoms or signs that parents defined as the child's usual starting point before development of severe LRTI. These episodes may not have led to an exacerbation episode as we defined in our inclusion criteria, so severity of episodes, rescue therapy use, and time to next RTI episode may be significantly different by definition; therefore, we also decided to exclude this study.

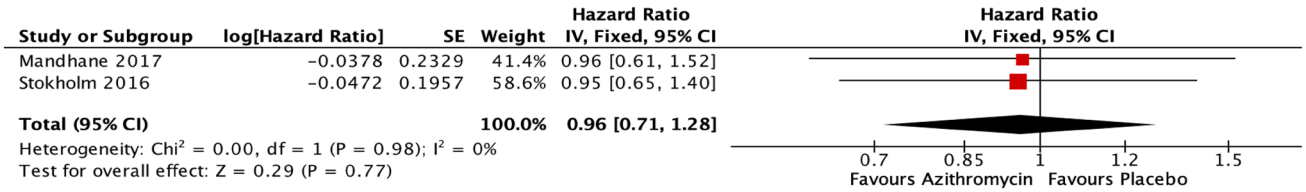

Fig. 3 Pooled hazard ratio and 95% CIs for the next episode of respiratory exacerbation in patients treated with azithromycin versus placebo. *HR* hazard ratio, *SE* standard error, *IV* inverse variance method, *CI* confidence interval, *Fixed* fixed-effects model

Different mechanisms of action of macrolides have been proposed when considering their use in acute asthma or wheezing exacerbations: antibiotic, anti-inflammatory, and immunomodulator. Macrolides may inhibit the synthesis and/or secretion of proinflammatory cytokines and modulate the immune reponse. It is presumed than this effect occurs via suppression of NF-kB and activator protein 1, affecting the production of cytokines IL-1β, IL-6, IL-8, TNF-α, reducing predominantly neutrofilic inflamation, and reducing the migration and oxidative burst activity in phagocytes [24, 33–39]. Also, several studies show a role of macrolides in viral infections [38, 40–42]. It is well known that asthma exacerbations are triggered frequently by infections [43], predominantly viral infections, but also by atypical bacteria or coinfections [44, 45].

In our review, the presence of viral or bacterial infections was evaluated in two studies [26, 27]. Stokholm et al. [27] found a pathogenic bacteria in 67% (mostly *Moraxella catarrhalis*) and virus in 43% (rhinovirus, RSV, and enteroviruses). Koutsoubari et al. [26] found 65% of positive tests with a predominance of rhinovirus, and two patients had serologically confirmed mycoplasma infection (one in each group of treatment, $p = 0.704$). These studies excluded patients with suspected pneumonia or elevated C-reactive protein, suggesting that the action of macrolides in reducing the duration of index episode or severity of symptoms is not only explainable by a misdiagnosis of pneumonia or co-infection with atypical bacteria during the exacerbation. Perhaps the anti-inflammatory action of macrolides had a role.

We did not find any study that reported antibiotic resistance outcomes. However, there is still serious concern about the potential widespread use of macrolides in these patients in the context of a worldwide increase in antibiotic resistance [46, 47]. In our review, we found no differences in AEs in the macrolides group versus controls; the most reported AE was gastrointestinal. A recent Cochrane systematic review [48] evaluating AEs in both adults and children taking macrolide versus placebo for any indication, reported an OR of 2.16 (95% CI 1.56–3.00) for gastrointestinal disorders not otherwise specified, with a number needed to harm (NNTH) of 12.

The present study has some limitations. First, only one [26] out of the three studies included school children with acute asthma exacerbation and this was the only study that performed lung function tests; therefore, we cannot directly apply these findings to schoolchildren with acute asthma exacerbation. The other two studies [27, 28] included preschoolers with a different definition of recurrent wheezing episodes, which represents frequent clinical presentation and is considered an important population of high asthma risk, even though the diagnosis of asthma could not be accurately done at this age. Second, there were differences in the basal treatment of patients included in the studies, suggesting also that we likely included patients with different severity of symptoms, although some studies [27, 28] reported no significant association between some outcomes and steroids (OCS or ICS) or montelukast. Third, the 'time to next exacerbation' outcome might be inaccurate because HRs may have been calculated with a different follow-up time. Fourth, microbiological assessment was different between studies, while some used culture for bacteria, others used PCR and serology. Fifth, we were unable to test our pre-established subgroup analysis because there were not enough reported data in specific age groups or severity of the exacerbation or sponsor (two studies [27, 28] were independently funded and the other did not mention funding), or atopic condition (only one study [27] reported data for this item).

5 Conclusion

We found limited evidence that macrolides used in children with acute asthma or wheeze exacerbation may reduce the duration and severity of the episode and may improve lung function. However, no difference in hospitalization, or reduction in the risk of a second episode was found. No study reported data for antibiotic resistance. Therefore, we suggest that a macrolide trial could be considered in children with acute asthma or recurrent wheezing exacerbations. The above cannot be extrapolated to patients with severe chronic symptoms. Future research should be oriented to properly identify and characterize the potential responder's group, the risk of antibiotic resistance development, intervention with non-antibiotic macrolides, and to compare the use of intermittent ICS versus macrolides.

Compliance with Ethical Standards

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

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Supplement to

Efficacy of macrolides on acute asthma or wheezing exacerbations in children with recurrent wheezing. A systematic review and meta-analysis.

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Pediatric Drugs, 2019

Detailed Search Strategy

1.- PUBMED – MEDLINE

randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) AND (("asthma"[MeSH Terms] OR "asthma"[All Fields]) OR "acute asthma"[All Fields] OR "asthma attack"[All Fields] OR "asthma exacerbation"[All Fields] OR "wheezing"[All Fields] OR (("respiratory sounds"[MeSH Terms] OR ("respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields] OR "wheezing"[All Fields]) OR exacerbation[All Fields]) OR "recurrent wheezer"[All Fields] OR "recurrent wheeze"[All Fields] OR "acute wheeze"[All Fields] OR "wheezing episode"[All Fields] OR "asthma episode"[All Fields] OR (("lung"[MeSH Terms] OR "lung"[All Fields]) AND ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "symptoms"[All Fields] OR "diagnosis"[MeSH Terms] OR "symptoms"[All Fields]) AND episodes[All Fields]) OR (ashtma[All Fields] AND like[All Fields] AND episodes[All Fields])) AND (("macrolides"[MeSH Terms] OR "macrolides"[All Fields]) OR ("azithromycin"[MeSH Terms] OR "azithromycin"[All Fields]) OR ("clarithromycin"[MeSH Terms] OR "clarithromycin"[All Fields]) OR ("erythromycin"[MeSH Terms] OR "erythromycin"[All Fields]) OR ("telithromycin"[Supplementary Concept] OR "telithromycin"[All Fields])) AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms])

2.- EMBASE – Elsevier

('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR cro
ssover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti) AND ('asthma' OR 'acute asthma' OR 'asthma attack' OR 'asthma exacerbation' OR 'wheezing' OR 'wheeze' OR 'recurrent wheezer' OR 'recurrent wheeze' OR 'acute wheeze' OR 'wheezing episode' OR 'asthma episode' OR 'lung symptoms') AND ('macrolides' OR 'azithromycin' OR 'clarithromycin' OR 'erythromycin' OR 'telithromycin') AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim)

3.- Cochrane Central Register of Controlled Trials (CENTRAL)

('asthma' OR 'acute asthma' OR 'asthma attack' OR 'asthma exacerbation' OR 'wheezing' OR 'wheeze' OR 'recurrent wheezer' OR 'recurrent wheeze' OR 'acute wheeze' OR 'wheezing episode' OR 'asthma episode' OR 'lung symptoms') AND ('macrolides' OR 'azithromycin' OR 'clarithromycin' OR 'erythromycin' OR 'telithromycin')

4.- Latin American and Caribbean Health Science Literature (LILACS) – BIREME (bvsalud.org)

tw:((tw:(("asthma" OR "asma" OR "acute asthma" OR "asma agudo" OR "crisis de asma" OR "crisis asmatica" OR "ataque de asma" OR "asthma attack" OR "exacerbacion asmatica" OR "asthma exacerbation" OR "sibilancia" OR "sibilancias recurrentes" OR "sibilante recurrente" OR "wheezing" OR "wheeze" OR "recurrent wheezer" OR "recurrent wheeze" OR "acute wheeze" OR "wheezing episode" OR "episodio de sibilancia" OR "asthma episode" OR "lung symptoms") AND ("macrolides" OR "macrolidos" OR "azithromycin" OR "azitromicina" OR "clarithromycin" OR "claritromicina" OR "erythromycin" OR "eritromicina" OR "telithromycin" OR "telitromicina")))) AND (db:("LILACS") AND type_of_study:("clinical_trials"))

5.- CINAHL – EBSCO

('asthma' OR 'acute asthma' OR 'asthma attack' OR 'asthma exacerbation' OR 'wheezing' OR 'wheeze' OR 'recurrent wheezer' OR 'recurrent wheeze' OR 'acute wheeze' OR 'wheezing episode' OR 'asthma episode' OR 'lung symptoms') AND ('macrolides' OR 'azithromycin' OR 'clarithromycin' OR 'erythromycin' OR 'telithromycin') Applied Filters: newborn to 18 years.

6.- Clinicaltrials.gov

Interventional Studies | 'asthma' OR 'acute asthma' OR 'asthma attack' OR 'asthma exacerbation' OR 'wheezing' OR 'wheeze' OR 'recurrent wheezer' OR 'recurrent wheeze' OR 'acute wheeze' OR 'wheezing episode' OR 'asthma episode' OR 'lung symptoms' | 'macrolides' OR 'azithromycin' OR 'clarithromycin' OR 'erythromycin' OR 'telithromycin' | Child
Applied Filters: Interventional /Child (birth–17)