Azithromycin and Other Macrolides for Prevention of Bronchopulmonary Dysplasia: A Systematic Review and Meta-Analysis

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Key Words

Azithromycin · Bronchopulmonary dysplasia · Macrolides · Preterm infants

Abstract

Background and Objective: *Ureaplasma* spp. infection has been associated with bronchopulmonary dysplasia (BPD) in preterm infants. Macrolides have been used for the treatment of *Ureaplasma* spp. infection, with an intention to prevent BPD. The objective of this meta-analysis is to evaluate the use of macrolides in the prevention of BPD in preterm infants. **Methods:** We searched MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials, abstracts of the major pediatric society meetings and bibliographies of retrieved articles. We included randomized controlled trials assessing the effects of macrolides therapy on BPD in preterm infants. A random/fixed-effect model was used to synthesize predefined outcomes. **Results:** Six studies involving 469 preterm infants were eligible for the analysis. Macrolides when used prophylactically (4 studies) did not show significant reduction in BPD (risk ratio, RR, 0.88, 95% confidence interval, CI, 0.75–1.03), death (RR 0.89, 95% CI 0.79–1.01) or in the composite outcome of BPD/death. Similarly, there was no significant reduction in BPD (RR 0.64, 95% CI 0.31–1.31) or

the composite outcome of BPD/death (RR 0.41, 95% CI 0.05–3.13), when macrolides were used in *Ureaplasma*-positive infants. However, prophylactic azithromycin therapy (3 studies) was associated with significant reduction in BPD (RR 0.83, 95% CI 0.71–0.97; number needed to treat, NNT, 10) and composite outcome of BPD/death (RR 0.86, 95% CI 0.77–0.97; NNT 10). **Conclusion:** This meta-analysis demonstrates prophylactic azithromycin therapy was associated with statistically significant reduction in BPD and the composite outcome of BPD/death in preterm infants. However, given the limited information on pharmacokinetics and potential harmful effects, further studies should be done before routine use of azithromycin in the neonatal population.

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Introduction

Bronchopulmonary dysplasia (BPD) remains a major health problem in preterm infants resulting in increased health care costs, prolonged hospital stay, and effects on subsequent growth and neurodevelopment [1]. The incidence of BPD vary among different centers, ranging from 44 to 77% in infants weighing <1,000 g [2]. Chorioamnionitis is an important risk factor associated with de-

velopment of BPD [3]. *Ureaplasma* spp. are the most common organisms isolated from women with chorioamnionitis [4, 5] and have been associated with increased risk for preterm labor. *Ureaplasma* spp. colonization has been associated with the development of pulmonary inflammation and BPD in preterm infants [6]. Two meta-analyses have suggested an association between *Ureaplasma* infection and the development of BPD [7, 8]. Intrauterine infection with *Ureaplasma* spp. can lead to altered lung development, prolonged inflammatory response and increased fibrotic reaction in animals [9, 10]. *Ureaplasma* infection induces production of tumor necrosis factor- α and interleukin-6 [11] and also causes apoptosis of human type 2 lung epithelial cells and lung macrophages [12]. Apart from BPD, *Ureaplasma* has also been associated with retinopathy of prematurity [13], intraventricular hemorrhage [14, 15], necrotizing enterocolitis (NEC) [16] and adverse neurodevelopmental outcome [17]; all these associations could be attributed to the ability of *Ureaplasma* to elicit an inflammatory reaction.

Macrolides are antimicrobial agents with anti-inflammatory actions, which may play a role in preventing BPD [18, 19]. The commonly used macrolides for treatment of *Ureaplasma* spp. in the neonatal period include erythromycin, azithromycin and clarithromycin. Macrolides have been successfully used in treatment of inflammatory lung diseases such as chronic obstructive pulmonary disease and cystic fibrosis. There is limited evidence regarding the use of macrolides for the treatment of *Ureaplasma* colonization or the prophylactic use (irrespective of *Ureaplasma* culture status) for the prevention of BPD in preterm infants. Few clinical trials have reported the effect of macrolides in the prevention of BPD with conflicting results [20–25]. A Cochrane review on erythromycin for the prevention of BPD included 2 studies and reported no significant reduction in BPD or death [26]. Since then, 4 randomized control trials have been published between 2007 and 2013 using various types of macrolides for prevention of BPD [22–25]. The objective of this systematic review and meta-analysis is to evaluate the current evidence on the use of macrolides in the prevention of BPD in preterm infants.

Material and Methods

Study Eligibility

We included randomized or quasi-randomized controlled trials evaluating either prophylactic or therapeutic use of macrolides for the prevention of BPD and/or death in preterm infants. We

excluded review articles, case reports, meta-analyses, pharmacokinetic studies, studies showing only clearance of *Ureaplasma*, use of macrolides for obstetric purposes and for feeding intolerance in infants.

Data Sources

We did a comprehensive search in the following computerized biomedical databases: Ovid MEDLINE (1946–2013), EMBASE (1974–2013), Cochrane Central Register of Controlled Trials (December 2013), International Pharmaceutical Abstracts (1970–2013), abstracts from Pediatric Academic Society meeting and European Society for Pediatric Research (last 10 years). Searches were supplemented by scanning bibliographies. We used boolean operators (and, or, not) as needed. We performed text word/MeSH and explode search strategy to optimize the literature retrieval. We used the following keywords: Infant, Premature/[preterm infant terms], exp Macrolides/[macrolide terms] (erythromycin, azithromycin, clarithromycin, roxithromycin, and troleandomycin), BPD/bronchopulmonary dysplasia, CLD/chronic lung disease. We limited our search to human studies only. No language restrictions were applied.

Study Selection and Data Extraction

All the abstracts identified by online searches were screened by two reviewers (V.N., P.L.) to determine the eligibility for further review. Data extraction was performed independently by the two investigators (V.N., P.L.) by using a standard data collection form. Discrepancies in eligibility screening, data extraction, data entry and analysis were resolved by discussion. We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for study selection process.

Study Quality Assessment

Two investigators independently assessed the quality of each study using the Cochrane collaboration's tool for assessing risk of bias in randomized trials. Methodological quality was evaluated by assessing selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), attrition bias (incomplete outcome data), detection bias (blinding of outcome), reporting bias, and other possible sources of bias. Studies were considered at low risk of bias if they were at low risk of both selection and allocation bias and one of detection, performance, or reporting bias. Studies were otherwise classified as high risk.

Data Synthesis

We used Revman 5.2 software for all our statistical analysis. We performed the analyses to evaluate the effect of macrolides on the incidence of BPD, death and the composite outcome of BPD/death when used prophylactically (irrespective of *Ureaplasma* status) and in *Ureaplasma*-positive preterm infants (therapeutic use). We also performed a separate analysis on the effect of azithromycin on these outcomes. All the treatment effects of categorical variables were reported as risk ratio (RR) with 95% confidence interval (CI) using Mantel-Haenszel method. I^2 statistic was used to assess the heterogeneity (I^2 ranges between 0 and 100%, with lower values representing less heterogeneity). We used a random-effect model if there was significant heterogeneity ($I^2 \geq 50\%$) and a fixed-effect model when I^2 was less than 50%.

Fig. 1. Flow diagram for selection of studies.

Results

A total of 209 abstracts were screened. Six studies met inclusion criteria and were included in the meta-analysis. A manual search of references cited in these articles did not yield new eligible articles. Figure 1 shows the flow diagram of studies identified in the PRISMA format. Of the 6 studies, 4 examined the effect of prophylactic use of macrolides on the incidence of BPD [20, 22–24]. Ballard et al. [23] also evaluated the effect of azithromycin in a subgroup of infants who were *Ureaplasma* positive. A total of 3 studies reported the effect of macrolides on the incidence of BPD among *Ureaplasma*-positive preterm infants [21, 23, 25].

Study Characteristics

The characteristics of the included study are shown in table 1. Three studies compared azithromycin with placebo [22–24]. Two studies compared erythromycin with

placebo [20, 21] and only one study compared clarithromycin with placebo [25]. Two studies specifically used macrolides in infants colonized with *Ureaplasma* [21, 25] and remaining studies used macrolides prophylactically in infants irrespective of *Ureaplasma* status.

Table 2 shows the comparison of the study quality. Only 2 studies were of high quality satisfying ≥ 4 out of 8 criteria [23, 24], and the remaining studies were of either low or unclear quality. There was no significant publication bias as assessed by the funnel plot (fig. 2).

Primary Outcomes

Effect of Prophylactic Azithromycin on Outcomes

Three studies were included in the analysis [22–24]. The prophylactic azithromycin use demonstrated a significant reduction in BPD (RR 0.83, 95% CI 0.71–0.97; number needed to treat, NNT, 10) and the composite outcome of BPD/death (RR 0.86, 95% CI 0.77–0.97; NNT 10;

Table 1. Characteristics of the trials included in the analysis

Source	Inclusion criteria	<i>Ureaplasma</i> colonization rate and detection technique	Macrolides used	Dosage and duration	Macrolide initiation	Primary outcome
Jonsson et al. [21], Sweden	<30 weeks, ventilated and <i>Ureaplasma</i> positive	19%; tracheal and nasopharyngeal aspirate cultures	erythromycin	40 mg/kg/day × 10 days	as soon as cultures were available (mean: 7 days)	BPD, clearance of colonization with <i>Ureaplasma</i>
Lyon et al. [20], Edinburgh	<30 weeks and ventilated	15%; tracheal aspirate cultures and PCR	erythromycin	45 mg/kg/day × 7 days	at birth	BPD, cytokine levels in tracheal aspirates
Ballard et al., USA [22]	BW <1,000 g and ventilated	19%; tracheal aspirate cultures	azithromycin	10 mg/kg/day × 7 days ¹	0–72 h of age	BPD
Ballard et al. [23], USA	BW <1,250 g and ventilated	35%; tracheal aspirate PCR	azithromycin	10 mg/kg/day × 7 days ¹	0–72 h of age	BPD
Ozdemir et al. [25], Turkey	BW 750–1,250 g and <i>Ureaplasma</i> culture positive	33%; nasopharyngeal swab cultures	clarithromycin	20 mg/kg/day × 10 days	0–72 h of age	BPD
Gharehbaghi et al. [24], Iran	<32 weeks and <1,500 g	sampling not done	azithromycin	10 mg/kg/day × 7 days followed by 5 mg/kg/day × 7 days	day 7 of life	BPD

IMV = Intermittent mandatory ventilation; BW = body weight. ¹ Followed by 5 mg/kg/day until the infant no longer required IMV or supplemental O₂ to a maximum of 6 weeks.

Table 2. Risk of bias assessment

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias; patient-reported outcomes)	Blinding of outcome assessment (detection bias; all-cause mortality)	Incomplete outcome data (attrition bias; short term)	Incomplete outcome data (attrition bias; long term)	Selective outcome reporting (reporting bias)
Jonsson et al. [21]	–	–	–	–	–	–	–	–
Lyon et al. [20]	+	+	?	–	–	–	–	–
Ballard et al. [22]	+	+	?	?	?	?	?	–
Ballard et al. [23]	+	+	?	+	+	–	–	–
Ozdemir et al. [25]	–	+	?	?	?	?	?	?
Gharehbaghi et al. [24]	+	+	+	+	+	–	–	?

fig. 3, 4). There was no significant reduction in mortality (RR 1.00, 95% CI 0.66–1.50; fig. 5).

Effect of Prophylactic Macrolides on Outcomes

Four studies (3 studies with azithromycin and 1 study with erythromycin) were included involving 373 infants, 191 infants in the macrolides group and 182 infants in the

control group [20, 22–24]. A higher proportion of neonates in the control group developed BPD as compared with macrolides group (55 vs. 49%). However, there was no statistically significant reduction in BPD (RR 0.88, 95% CI 0.75–1.03), death (RR 1.00, 95% CI 0.68–1.48) or the composite outcome of BPD/death (RR 0.89, 95% CI 0.79–1.01; fig. 6–8).

Fig. 2. Funnel plot for publication bias.

Fig. 3. Forest plot for effect of prophylactic azithromycin on the incidence of BPD.

Fig. 4. Forest plot for effect of prophylactic azithromycin on BPD/death.

Fig. 5. Forest plot for effect of prophylactic azithromycin on death.

Fig. 6. Forest plot for effect of prophylactic macrolides on the incidence of BPD.

Fig. 7. Forest plot for effect of prophylactic macrolides on death.

Fig. 8. Forest plot for effect of prophylactic macrolides on BPD/death.

Fig. 9. Forest plot for effect of macrolides on the incidence of BPD among *Ureaplasma*-positive infants.

Effect of Macrolides in *Ureaplasma*-Positive Infants

In this analysis, 3 studies (using erythromycin, azithromycin, and clarithromycin) were included with a total of 156 infants [21, 23, 25]. The meta-analysis did not demonstrate a reduction of BPD (RR 0.64, 95% CI 0.31–1.31), death (RR 0.84, 95% CI 0.39–1.81) or the composite outcome of BPD/death (RR 0.41, 95% CI 0.05–3.13; fig. 9–11). Only 2 studies were available for the analysis of death and the composite outcome of BPD/death [23, 25]. Jonsson et al. [21] reported one neonatal death, but it was unclear if the infant belonged to the macrolides or control group.

Secondary Outcomes

Two important secondary outcomes of interest were the duration of ventilation and the hospital stay. There

were no uniform secondary outcomes reported in these studies except for the duration of ventilation. However, analysis was challenging due to different formats of reporting. We could not combine the results as some studies reported the duration of ventilation [22–24] as mean while others reported it as median [20, 21]. In the study by Lyon et al. [20], there was no significant difference in inflammatory markers between the two groups, and none of the other trials have studied the role of inflammatory markers. We also examined whether use of macrolides for a relatively longer period led to superadded bacterial or fungal infections. Only 4 studies reported sepsis data with incomplete description of sepsis [22–25]. Hence, analysis was not possible.

Fig. 10. Forest plot for effect of macrolides on death among *Ureaplasma*-positive infants.

Fig. 11. Forest plot for effect of macrolides on BPD/death among *Ureaplasma*-positive infants.

Discussion

To the best of our knowledge, this is largest systematic review on this topic to answer a clinically important question. We analyzed the therapeutic use of macrolides in *Ureaplasma*-positive preterm infants and prophylactic macrolide treatment separately. We also analyzed the effect of most commonly used macrolide, azithromycin, on the incidence of BPD and composite outcome of BPD/death.

The present meta-analysis demonstrates statistically significant reduction in the BPD or composite outcome of BPD/death when azithromycin was used prophylactically in preterm infants. Ten infants need to be treated prophylactically with azithromycin to prevent one case of BPD. However, on combining all the studies, irrespective

of the type of macrolides used, we observed no significant reduction in BPD, although there was a trend towards reduction in BPD and composite outcome of BPD/death.

The previous Cochrane review on use of erythromycin for prevention of BPD included 2 studies, one with therapeutic use of erythromycin to *Ureaplasma*-positive infants and another given prophylactically [26]. We did not perform separate analysis, as there were no new studies using erythromycin. Similarly, we could not do meta-analysis for clarithromycin as only one study was identified.

Clinical isolates of *Ureaplasma* have been found to be susceptible to other macrolides such as azithromycin and clarithromycin with in vitro antibacterial activity superior to that of erythromycin [27]. Azithromycin and clarithromycin achieve better drug concentration in lung ep-

ithelium and alveolar macrophages than erythromycin [28]. In a recent systematic review of 24 trials in pediatric upper respiratory tract infection, clarithromycin was therapeutically equivalent to other antibiotics, but has better bacteriological eradication and lower adverse effects [29].

The study by Ballard et al. [23] contributed to almost one third of the population in this meta-analysis. They used azithromycin in the dose of 10 mg/kg/day for a maximum duration of 6 weeks and did not observe significant reduction in the BPD. This is probably explained by the fact that azithromycin at this dose may not be effective in *Ureaplasma* clearance and suppression of inflammatory cytokines [30]. A recent pharmacokinetic study of azithromycin showed 20 mg/kg/day for 3 days might have better *Ureaplasma* clearance and anti-inflammatory action as well as safety [31]. In vitro susceptibility studies on *Ureaplasma* showed that clarithromycin was the most active macrolide with minimal inhibitory concentration (MIC) 0.25 µg/ml as compared to erythromycin and azithromycin with MIC of 2 µg/ml [32].

The main limitation of our analysis is due to primary studies included and their methodologies. Of the 6 studies included in the analysis, the 2 erythromycin studies were published 16 years ago with lots of changes in neonatal intensive care unit practice and BPD rate since that time.

The choice and dosage of macrolides were empirically chosen and were not based on any pharmacokinetic studies. The types of macrolide, their dosages, method of *Ureaplasma* detection, the time of initiation of macrolides and duration of treatment varied among the studies. Lyon et al. [20], Jonsson et al. [21], and Ballard et al. [22] employed tracheal aspirate culture for detection of *Ureaplasma*. In the subsequent study by Ballard et al. [23], they used polymerase chain reaction (PCR) techniques on tracheal aspirates and Ozdemir et al. [25] used nasopharyngeal aspirate for *Ureaplasma* detection. Except for one study [23], most of the studies included in the analysis were of small sample size and only two studies were of high quality [23, 24]. Most of the studies did not report the potential side effects such as nosocomial sepsis and NEC. There was limited information on the duration of hospital stay and feeding intolerance. Randomized trials that used prophylactic macrolides showed a trend towards significance, possibly explaining the fact that early control of infection/inflammation may play a role in prevention of BPD. However, this may be reflective of the high prevalence of BPD (84%) in the included studies and 2 out of 3 studies are from the same center [22, 23].

Perinatal infection is an independent risk factor for BPD. Treatment of perinatal infection with antibiotics may reduce the neonatal morbidities by prolonging pregnancy or reducing infection-related inflammation. A recent Cochrane review on antibiotics for preterm premature rupture of membrane (PPROM) showed only short-term benefits, and there was no difference in the incidence of BPD [33]. Though *Ureaplasma* is the most common commensal in the maternal genital tract, about 22% of mothers with PPRM or preterm labor will have evidence of *Ureaplasma* infection. Therefore, routine treatment of all pregnant women with PPRM or preterm labor will in many cases be unnecessary. Although the NNT in this meta-analysis was 10, the incidence of BPD is variable and only a third of the preterm infants are colonized with *Ureaplasma* spp., clinicians should be cautious while using the prophylactic macrolide therapy as it may lead to unnecessary treatment of many preterm infants. Prolonged antibiotic therapy should be avoided in preterm neonates because prolonged antibiotic exposure has been associated with increased rates of NEC, late-onset sepsis and death [34].

Several studies in adults have highlighted the association between macrolide use and cardiovascular events, notably arrhythmias and death [35, 36]. In 2013, the United States Food and Drug Administration issued drug alert regarding the use of azithromycin especially in high-risk patients such as those with known prolonged QTc syndromes, on drugs known to prolong QTc and proarrhythmogenic conditions. These events have not been described in the neonatal literature. However, the physicians caring for preterm infants should be aware of this potential side effect. In a recent study by Lund et al. [37], use of macrolides, notably erythromycin, during the first 14 days of life was significantly associated with infantile hypertrophic pyloric stenosis. Until further studies are available, caution is required for routine clinical use of macrolides in BPD prevention.

Since BPD is a multifactorial disease, it is unlikely that a single treatment modality will be completely effective in preventing BPD. It is essential to conduct pharmacokinetic studies to find the macrolide of choice, dosage schedule, formulation and duration of treatment. Apart from the clinical outcomes, it is important to understand the anti-inflammatory and antimicrobial properties of macrolides, to study *Ureaplasma* clearance with macrolides as well as levels of inflammatory markers following treatment.

Conclusion

In this meta-analysis, azithromycin when given prophylactically is associated with reduction in BPD and BPD/death in preterm infants. However, studies combining all macrolides when used either prophylactically or therapeutically in *Ureaplasma*-colonized ventilated preterm infants did not reduce BPD or composite outcome of BPD/death. With infection/inflammation playing a major role in the pathogenesis of BPD and in the era

where no effective treatment for BPD exists, randomized control trials with macrolides are not unreasonable. However, high-quality pharmacokinetic studies are needed before routine use of azithromycin in the neonatal intensive care units.

Disclosure Statement

None.

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