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Azithromycin for Eradication of *Ureaplasma* and Prevention of Bronchopulmonary Dysplasia in Preterm Neonates in the Neonatal Intensive Care Unit

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Azithromycin has been explored as a treatment option for eradication of *Ureaplasma* and prevention of bronchopulmonary dysplasia (BPD) in preterm neonates. However, there is debate about the need for eradication of *Ureaplasma* and whether azithromycin is safe and efficacious for this indication. This literature review provides an overview of the evidence for use of azithromycin for eradication of *Ureaplasma* and prevention of BPD, including dosing and duration of azithromycin used in these studies. The literature search included articles published in the English language in Medline and PubMed from 1946 to January 2022. Relevant citations within identified articles were also reviewed. A total of 9 studies representing 388 neonates were included. The percentage of neonates that tested positive for *Ureaplasma* in these studies ranged from 18.6% to 57.1%. Azithromycin was initiated at <3 days of life in 8 studies (88.9%). Dosing was variable and ranged from 5 to 20 mg/kg/dose administered once daily, and the duration of treatment ranged from 1 to 35 days. Most studies used intravenous azithromycin. Overall, azithromycin was more efficacious than placebo at *Ureaplasma* eradication; however, most of these studies did not find a difference in the incidence of BPD between patients receiving azithromycin versus placebo. No adverse effects, specifically pyloric stenosis or QT interval prolongation, were noted in these studies.

ABBREVIATIONS aOR, adjusted odds ratio; AUC, area under the curve; BPD, bronchopulmonary dysplasia; BSID, Bayley Scales of Infant and Toddler Development; IV, intravenously; MIC, minimum inhibitory concentration; MV, mechanical ventilation; NICU, neonatal intensive care unit; PCR, polymerase chain reaction; PMA, postmenstrual age; PNA, postnatal age; QTc, corrected QT interval

KEYWORDS azithromycin; bronchopulmonary dysplasia; chronic lung disease; neonate; *Ureaplasma*

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Introduction

Ureaplasma is a commensal organism frequently identified as a colonizer in the maternal genitourinary tract. If maternal colonization is present, *Ureaplasma* can be transmitted from the mother to the neonate while *in utero* or during delivery. It has been reported that transmission from vaginally colonized mothers occurs in up to 38% of term infants and 95% of very low birth weight infants.[1,2] Transmission of *Ureaplasma* to the neonate can result in colonization of the respiratory tract, which can promote an inflammatory cascade in the lungs. This inflammatory response is believed to contribute to the development of bronchopulmonary dysplasia (BPD). Neonates with *Ureaplasma* colonization have been reported to have 2 times greater odds of receiving a diagnosis of BPD at 36 weeks postmenstrual age (PMA).[3] In addition, maternal colonization with *Ureaplasma* has also been associated with increased incidence of severe intraventricular hemorrhage, retinopathy of prematurity, and poorer neurodevelopmental outcomes in very preterm infants.[4]

Azithromycin has been evaluated as a potential option for the prevention of BPD because of its activity against *Ureaplasma* and its immunomodulatory effects that result in decreased production of proinflammatory cytokines.[5] However, there is much debate regarding the need for *Ureaplasma* eradication empirically with azithromycin and whether it should be considered a first-line option for prophylaxis or treatment.[6] In addition, there is no consensus on the azithromycin dosing regimen for this indication.[7] This review aims to describe the available literature regarding the efficacy and safety of azithromycin for treatment of *Ureaplasma* colonization and prevention of BPD, as well as the pharmacokinetic data to determine the appropriate dosing for this indication.

Literature Review

A literature search using Medline and PubMed was performed using the keywords *azithromycin*, *Ureaplasma*, and either *bronchopulmonary dysplasia* or *chronic lung disease*. Results were limited to human studies in neonatal patients published from 1946 to January 2022 and available in the English language.

One author (JLM) independently screened each article identified through the initial search. Articles were excluded if they were a case report or case series, review article or meta-analysis, were unrelated to the focus of this review, or lacked clinical details. Following initial review, all authors participated in the final selection process. All references of each article were screened for additional articles to include that may not have been identified in the initial search.

Results

A total of 36 articles were identified using the search strategy. Three additional studies were identified within the references of the screened articles. Overall, 30 articles were excluded for the following reasons: the articles were either a review article or meta-analysis (n = 15), unrelated to the specific review topic (n = 14), or lacked clinical details (n = 1). A total of 9 studies representing 388 neonates who received azithromycin were included in the review. This included 5 prospective studies focused on efficacy, 3 pharmacokinetic studies, and 1 long-term safety study. Tables 1 through 4 provide a summary of the included studies organized by the primary objective (i.e., prevention of BPD, eradication of *Ureaplasma*, pharmacokinetic evaluation, or long-term follow-up data).[8–16]

Efficacy of Azithromycin for Prevention of BPD. The efficacy of azithromycin for the prevention of BPD was evaluated as the primary objective in 4 studies, representing 226 premature neonates that received azithromycin and 217 that received placebo (Table 1).[8–11] Ballard et al[8] conducted a pilot study of prophylactic azithromycin versus placebo in extremely low birth weight neonates ≤72 hours of age within 12 hours of initiating mechanical ventilation. Nineteen patients received azithromycin 10 mg/kg every 24 hours intravenously (IV) or enterally (orally) for 7 days, followed by 5 mg/kg every 24 hours IV or orally for 35 days, and 16 patients received placebo. Tracheal aspirates were obtained at the time of randomization and prior to treatment. If a respiratory culture was positive for *Ureaplasma* or *Mycoplasma*, the patient was removed from the study. Eight patients (18.6%) were excluded from data analysis for this reason. For the remaining patients, there were no differences in incidence of BPD (64.3% versus 83.3%; p = 0.26), mortality (26.3% versus 25.0%; p = 0.9), or hospital length of stay (67 ± 40 versus 78 ± 50 days; p = 0.47) in the azithromycin versus placebo group, respectively. The only statistical difference noted by the authors was fewer patients in the azithromycin group received postnatal steroids to facilitate weaning off mechanical ventilation (MV; 31.5% versus 62.5%; p = 0.05).

As a follow-up to their initial pilot, Ballard et al[9] conducted a prospective, randomized, double-blind study of azithromycin versus placebo with a larger sample size (n = 220) of low birth weight neonates at ≤72 hours of age within 12 hours of initiating MV. One hundred eleven patients were randomized to receive azithromycin 10 mg/kg every 24 hours IV or orally for 7 days, followed by 5 mg/kg every 24 hours IV or orally for 35 days, and 109 were randomized to receive placebo. Treatment was initiated within 12 hours of life for 90% of study patients. Tracheal aspirates were obtained at the time of enrollment, again on day 3 of treatment, and weekly thereafter. Seventy-six patients (35.3%) tested positive for *Ureaplasma*, 31% (n = 33) of the azithromycin group and 40% (n = 43) of the placebo group. No difference in incidence of BPD (76% versus 84%; p = 0.2), mortality (18% versus 22%; p = 0.45), or hospital length of stay (73 ± 36 versus 69 ± 36 days; p = 0.51) was noted in the azithromycin versus placebo group. The odds of developing BPD were lower in the azithromycin group, when adjusting for gestational age, sex, *Ureaplasma* status, and bacterial sepsis, but they were not statistically significant (adjusted odds ratio [aOR], 0.46; 95% CI, 0.18–1.21). In the *Ureaplasma*-positive patients, there was no difference in clearance of *Ureaplasma* between azithromycin-treated versus placebo-treated patients at the end of treatment, with 95% of patients in both groups achieving eradication. However, there was a lower incidence of BPD in *Ureaplasma*-positive patients receiving azithromycin at 36 weeks PMA (73% vs 94%; p = 0.03), but no differences in mortality. For *Ureaplasma*-positive patients, those treated with azithromycin had reduced odds of developing BPD or death (aOR, 0.026; 95% CI, 0.001–0.618).

Another prospective, randomized, controlled clinical trial conducted by Gharehbaghi et al[10] evaluated oral azithromycin versus placebo in low birth weight neonates at day 7 of life. Fifty-six patients were randomized to receive azithromycin at 10 mg/kg orally every 24 hours for 7 days, followed by 5 mg/kg orally every 24 hours for 7 days, and 52 were randomized to receive placebo. Tracheal aspirates were not collected for this study; therefore, incidence of *Ureaplasma* could not be reported. Five patients (8.9%) in the azithromycin group were discharged from the hospital before 21 days of age; therefore, the mean ± SD duration of azithromycin therapy was 13.6 ± 1.5 days. A lower rate of BPD was noted in the azithromycin group versus placebo at 28 days (25% versus 40.4%; p = 0.04) and at 36 weeks PMA (5.4% versus 17.3%; p = 0.04).

Nunes et al[11] conducted a randomized, placebo-controlled study to evaluate the anti-inflammatory effects of azithromycin for prevention of MV-induced lung injury in 80 premature neonates. Forty patients received azithromycin 10 mg/kg IV every 24 hours for 5 days, and 40 patients received placebo. Blood was obtained prior to and 24 hours after completion of therapy to evaluate serum cytokine concentrations and detection of *Ureaplasma*. Patients who received azithromycin had a significantly greater reduction in interleukin-2 (−13.6; 95% CI, −23.2 to −3.9) and interleukin-8 (−1904; 95% CI, −3803 to −725) compared

Table 1. Summary of Studies With Efficacy of Azithromycin for the Prevention of Bronchopulmonary Dysplasia as Primary Objective[8–11]

Reference	Design	Population	Azithromycin Dose and Duration	Results
Ballard[8]	Prospective, pilot study (AZM, n = 19; placebo, n = 16)	AZM: GA: 25.6 ± 1.5 wk BW: 762 ± 94 g PNA: ≤3 days Placebo: GA: 25.3 ± 1.0 wk BW: 736 ± 103 g PNA: ≤3 days	10 mg/kg IV or PO* every 24 hr × 7 days, then 5 mg/kg IV or PO* every 24 hr × 35 days	*Ureaplasma positive*: 8 patients (18.6%) excluded because *Ureaplasma* positive at enrollment *Incidence of BPD:* No difference in BPD at 36 wk PMA with AZM versus placebo (64.3% versus 83.3%; p = 0.26) *Eradication of Ureaplasma*: not evaluated *Other outcomes*: No difference in mortality Shorter duration of MV and hospital LOS in AZM versus placebo Decreased postnatal steroid use in AZM versus placebo (31.5% versus 62.5%; p = 0.05) No difference in hospital readmission or days on O_2 between groups at CA of 20–24 mo *ADE*: no ADE with AZM observed *Developmental outcomes*: AZM exposed scored higher on expressive communication at 20–24 mo compared with the placebo (p = 0.03)
Ballard[9]	Prospective (AZM, n = 111; placebo, n = 109)	*AZM*: GA: 25.7 ± 1.5 wk BW: 803 ± 170 g PNA: ≤3 days Placebo: GA: 26.0 ± 1.6 wk BW: 810 ± 188 g PNA: ≤3 days	10 mg/kg IV or PO* every 24 hr × 7 days, then 5 mg/kg IV or PO* every 24 hr × 35 days	*Ureaplasma positive*: 35.3% of patients were *Ureaplasma* positive *Incidence of BPD*: No difference in BPD at 36 wk PMA in AZM versus placebo (76% versus 84%; p = 0.2) In *Ureaplasma*-positive patients (n = 71), lower incidence of BPD at 36 wk PMA in AZM versus placebo (73% versus 94%; p = 0.03) *Eradication of Ureaplasma*: No difference in clearance of *Ureaplasma* in *Ureaplasma*-positive patients treated with AZM versus placebo (84.8% versus 88.4%) *Other outcomes*: No difference in mortality, duration of MV, duration of supplemental O_2, hospital LOS between groups *ADE*: No ADE with AZM observed *Developmental outcomes*: not evaluated

(Table cont. on page 13)

with those receiving placebo, when controlling for gestational age, birth weight, and 5-minute Apgar score; however, the differences in interleukin-1β, interleukin-6, interleukin-10, and tumor necrosis factor were not statistically different between groups. Of the 40 patients in each group, 13 (32.5%) that received azithromycin and 17 (42.5%) that received placebo were noted to test positive for *Ureaplasma*. Of these, 46.1% of the azithromycin and 64.7% of the placebo patients continued to test positive for *Ureaplasma* after 5 days of treatment. When comparing outcomes for those who tested positive for *Ureaplasma*, there were no differences in any clinical outcomes, including percentage needing supplemental oxygen at postnatal age (PNA) of 28 days (50.0% versus 78.6%; p = 0.280) or at PMA of 36 weeks (41.7% versus 42.9%; p = 0.473) in the azithromycin versus the placebo group. However, the sample size for this analysis was very small, and

Table 1. Summary of Studies With Efficacy of Azithromycin for the Prevention of Bronchopulmonary Dysplasia as Primary Objective8–11 *(cont.)*

Reference	Design	Population	Azithromycin Dose and Duration	Results
Gharehbaghi[10]	Prospective (AZM, n = 56; control, n = 52)	AZM: GA: 29.8 ± 2.5 wk BW: 1177.1 ± 221.0 g PNA: 7 days *Control*: GA: 29.7 ± 2.3 wk BW: 1212.9 ± 235.7 g PNA: 7 days	10 mg/kg PO every 24 hr × 7 days, then 5 mg/kg PO every 24 hr × 7 days	*Rate of Ureaplasma positive*: Did not test for *Ureaplasma* colonization *Incidence of BPD:* Lower rate of BPD at 36 wk PMA in AZM versus placebo (5.4% versus 17.3%; p = 0.04) *Eradication of Ureaplasma*: Did not test for *Ureaplasma* colonization *Other outcomes*: Mean duration of need for supplemental O_2 was lower in the AZM group compared with the control (p = 0.01) No difference in hospital LOS between groups *ADE*: No ADE with AZM observed *Developmental outcomes*: not evaluated
Nunes[11]	Prospective, placebo-controlled (AZM, n = 40; placebo, n = 40)	*AZM*: GA: 28.6 ± 2.99 wk BW: 1090 ± 575 g PNA: ≤3 days *Placebo*: GA: 27.1 ± 2.31 wk BW: 896 ± 268 g PNA: ≤3 days	10 mg/kg IV every 24 hr × 5 days	*Rate of Ureaplasma positive*: 37.5% of patients were *Ureaplasma* positive *Incidence of BPD:* No difference in O_2 dependency at 36 wk PMA in AZM versus placebo (28.1% versus 31.0%; p = 1.00) In *Ureaplasma*-positive patients that survived (n = 28), no difference in O_2 dependency at 36 wk PMA in AZM versus placebo (41.7% versus 42.9%; p = 0.473) *Eradication of Ureaplasma*: Eradication occurred in 53.8% of AZM and 35.3% of placebo group 24 hr after completion of treatment *Other outcomes*: AZM group had reduced risk of death (RR, 0.53; 95% CI, 0.28–0.98) and combined outcome of death with O_2 dependency at 28 days (RR, 0.71; 95% CI, 0.58–0.87) Significant reduction in plasma IL-2 (p = 0.044), IL-8 (p = 0.006), and IL-10 (p = 0.032) concentrations from baseline in the AZM group *ADE*: No ADE with AZM observed *Developmental outcomes*: not evaluated

ADE, adverse drug event; AZM, azithromycin; BPD, bronchopulmonary dysplasia; BW, birth weight; GA, gestational age; IL, interleukin; IV, intravenous; LOS, length of stay; MV, mechanical ventilation; O_2, oxygen; PMA, postmenstrual age; PNA, postnatal age

* Changed to PO when receiving full enteral feeds.

there is risk for type 2 error. A Poisson regression was used to evaluate risk for development of various neonatal outcomes when controlling for gestational age, birth weight, and 5-minute Apgar score for all 80 patients, regardless of *Ureaplasma* status. In this analysis, azithromycin use was associated with a 47% reduction in death (RR, 0.53; 95% CI, 0.28–0.98) and 29% reduction in risk for the combined outcome of death with supplemental oxygen at PNA of 28 days (RR, 0.71; 95% CI, 0.58–0.87); however, there was no difference in risk for supplemental oxygen at PNA of 28 days (RR, 0.77; 95% CI, 0.56–1.06) or PMA of 36 weeks (RR, 1.33; 95% CI, 0.64–2.79), or the combined outcome of death with supplemental oxygen at PMA

Table 2. Summary of Study With Eradication of *Ureaplasma* as the Primary Objective[12]

Reference	Design	Population	Azithromycin Dose and Duration	Results
Viscardi[12]	Prospective, placebo-controlled (AZM, n = 60; placebo, n = 61)	*AZM*: GA: 26.2 ± 1.4 wk BW: 895 ± 215 g PNA: 58.5 ± 23.1 hr *Placebo*: GA: 26.2 ± 1.4 wk BW: 903 ± 245 g PNA: 56.2 ± 19.4 hr	20 mg/kg IV every 24 hr × 3 days	*Rate of Ureaplasma positive*: 36.3% of patients were *Ureaplasma* positive *Incidence of BPD:* No difference in BPD at 36 wk PMA in AZM versus placebo (45% versus 33%; p = 0.28) In *Ureaplasma*-positive patients (n = 44), no difference in BPD at 36 wk PMA in AZM versus placebo (47% versus 38%; p = 0.49) *Eradication of Ureaplasma*: Eradicated in 100% of AZM versus 16% of placebo group (p < 0.001) 84% of placebo group were culture-positive at ≥1 follow-up time-point versus 0% in AZM group *Other outcomes*: No difference in survival at discharge, duration of MV, duration of O_2 support, or LOS between groups *ADE*: No ADE with AZM observed *Developmental outcomes*: not evaluated

ADE, adverse drug event; AZM, azithromycin; BPD, bronchopulmonary dysplasia; BW, birth weight; GA, gestational age; IV, intravenous; LOS, length of stay; MV, mechanical ventilation; O_2, oxygen; PMA, postmenstrual age; PNA, postnatal age

of 36 weeks (RR, 0.80; 95% CI, 0.54–1.19).

Efficacy of Azithromycin for the Eradication of *Ureaplasma*. The efficacy of azithromycin for eradication of *Ureaplasma* has been evaluated as the primary objective in only 1 study. (Table 2).[12] Viscardi et al[12] conducted a prospective, randomized, double-blind study that included preterm neonates who were <72 hours of age. Sixty patients were randomized to receive azithromycin 20 mg/kg IV every 24 hours for 3 days and 61 patients to receive placebo. Two tracheal aspirates, at least 2 hours apart, and 1 nasopharyngeal sample were obtained from intubated patients, and 2 nasopharyngeal samples, 2 hours apart, were obtained in non-intubated infants. Samples were sent for culture and polymerase chain reaction (PCR) and eradication was defined as 3 negative cultures after treatment. *Ureaplasma* was detected in 19 (31.7%) randomized to azithromycin and 25 (41.0%) randomized to placebo. In those that were positive for *Ureaplasma*, eradication occurred in a greater percentage of azithromycin versus placebo patients, 100% versus 16% (p ≤ 0.001). In patients with lower respiratory tract *Ureaplasma* colonization (n = 21), only 1 of 11 placebo patients (9.1%) achieved eradication, whereas eradication occurred in all 10 azithromycin patients (p < 0.001). The incidence of BPD was evaluated as a secondary objective, and no difference in BPD was observed between all patients treated with azithromycin versus placebo, 45% versus 33% (p = 0.28) or when specifically evaluating *Ureaplasma*-positive patients, 47% versus 38% (p = 0.49).

Pharmacokinetic and Clinical Outcome Studies of Azithromycin. The pharmacokinetics of azithromycin for the prevention of BPD have been explored in 3 studies representing 42 patients (Table 3).[13–15] All 3 of the pharmacokinetic studies were conducted by the same research group and built upon one another.[13–15] The initial study evaluated the pharmacokinetics of a single 10 mg/kg IV dose of azithromycin in 12 premature neonates.[13] The authors of this study concluded that neither a single 10 mg/kg IV dose nor 10 mg/kg IV every 24 hours for 3 days would provide adequate serum azithromycin concentrations for efficacy if assuming a minimum inhibitory concentration $(MIC)_{90}$ of 4 mcg/mL and MIC_{50} of 1 mcg/mL. This was also confirmed clinically as 43% of patients were determined to have failed treatment with positive posttreatment cultures. In addition, no appreciable effects were noted when evaluating tracheal aspirate cytokine concentrations at baseline and after treatment. After the single 10 mg/kg IV dose was deemed to be inadequate for *Ureaplasma* eradication, a second pharmacokinetic study was conducted to evaluate the safety of a single 20 mg/kg IV dose in 13 premature neonates.[14] *Ureaplasma* eradication was achieved 21 days after dose in 100% of patients that received a single 20 mg/kg azithromycin dose. For the pharmacokinetic analysis, data from these 13 patients were combined with data for the 12 patients that received a single 10 mg/kg dose from their previous study.[13] Serum concentrations were obtained at 0 to 1, 1 to 4, 6 to 8, 24 to 48, 48 to 96, and 96 to 144 hours after dose. Population modeling and simulations

Table 3. Summary of Pharmacokinetic and Clinical Outcome Studies[13–15]

Reference	Design	Population	Azithromycin Dose and Duration	Results
Hassan[13]	Pharmacokinetic pilot study (n = 12)	GA: 26.0 ± 1.0 wk BW: 855 ± 276 g PNA: 47.0 ± 28.0 hr	10 mg/kg IV × 1 dose	*Pharmacokinetic data:* Half-life of 58 hr in 1-kg neonate 10 mg/kg × 1 dose and 10 mg/kg every 24 hr for 3 days provides inadequate concentrations *Rate of Ureaplasma positive:* 57.1% of patients were *Ureaplasma* positive *Incidence of BPD:* 60% of *Ureaplasma*-positive and 17% of *Ureaplasma*-negative patients developed BPD at PMA of 36 wk *Eradication of Ureaplasma*: In *Ureaplasma*-positive patients (n = 8), eradication occurred in 57% of patients at 21 days PNA *Other outcomes:* AZM had no effect on tracheal aspirate inflammatory cytokines *ADE*: No ADE with AZM observed *Developmental outcomes*: not evaluated
Viscard[114]	Prospective, open label, pharmacokinetic (n = 13)	GA: 25.6 ± 1.2 wk BW: 870 ± 116 g PNA: 64.9 ± 30.3 hr	20 mg/kg IV × 1 dose	*Pharmacokinetic data*: AUC_{24}/MIC_{90} for a single 20 mg/kg dose is 7.5 hr Simulations of 20 mg/kg every 24 hr for 3 days suggest adequate concentrations achieved for ≥96 hr after first dose *Rate of Ureaplasma positive:* 54% of patients were *Ureaplasma* positive *Incidence of BPD:* 14% of *Ureaplasma*-positive patients and 50% of *Ureaplasma*-negative patients developed BPD at PMA of 36 wk (p = 0.164) *Eradication of Ureaplasma*: In *Ureaplasma*-positive patients, no patients had a positive PCR or culture at 21 days PNA *Other outcomes*: not evaluated *ADE*: No ADE with AZM observed *Developmental outcomes*: not addressed
Merchan[15]	Prospective, open label, pharmacokinetic (n = 15)	*Ureaplasma* positive: GA: 26.2 ± 1.2 wk BW: 856 ± 202 g PNA: 60 hr (IQR, 35–76) *Ureaplasma* negative: GA: 26.3 ± 1.7 wk BW: 929 ± 285 g PNA: 51 hr (IQR, 41–66)	20 mg/kg IV every 24 hr × 3 days	*Pharmacokinetic data*: Half-life of 69 hr in 1-kg neonate AUC_{24}/MIC_{90} of 4 hr Plasma concentrations mostly maintained between 2 and 8 mcg/mL for 120 hr after first dose with 20 mg/kg every 24 hr × 3 days *Rate of Ureaplasma Positive:* 46.7% of patients were *Ureaplasma* positive *Incidence of BPD:* 43% of *Ureaplasma*-positive patients and 12.5% of *Ureaplasma*-negative patients developed BPD at PMA of 36 wk (p = NS) *Eradication of Ureaplasma:* In *Ureaplasma*-positive patients, 14.3% PCR positive and 0% culture positive at 4–5 days after last dose of AZM *Other outcomes:* None of survivors (n = 14) hospitalized for respiratory illness at 6 mo CA *ADE*: No ADE with AZM observed *Developmental outcomes*: not evaluated

ADE, adverse drug event; AUC: area under the curve; AZM, azithromycin; BPD, bronchopulmonary dysplasia; BW, birth weight; GA, gestational age; IV, intravenous; MIC, minimum inhibitory concentration; PCR, polymerase chain reaction; PMA, postmenstrual age; PNA, postnatal age

Table 4. Summary of Study With Long-Term Outcomes as the Primary Objective[16]

Reference	Design	Population	Azithromycin Dose and Duration	Results
Viscardi[16]	Prospective, placebo-controlled (AZM, n = 60; placebo, n = 61)	AZM: GA: 26.2 ± 1.4 wk BW: 895 ± 215 g CA: 23.7 ± 2.1 mo (n = 48) Placebo: GA: 26.2 ± 1.4 wk BW: 903 ± 245 g CA: 23.7 ± 2.1 mo (n = 46)	20 mg/kg IV every 24 hr × 3 days	Rate of *Ureaplasma* positive: 35.5% of patients were *Ureaplasma* positive Incidence of death or serious respiratory morbidity at 22–26 mo CA: No difference between AZM and placebo group (34.8% versus 30.5%; p = 0.67) In *Ureaplasma*-positive patients (n = 44), increased rate in AZM versus placebo patients (52.6% versus 28.8%; p = 0.064) In *Ureaplasma*-positive patients (n = 44), greater serious respiratory morbidity in AZM versus placebo group (44.3% versus 15.2%; p = 0.036) Other outcomes at 22–26 mo CA: No difference in albuterol, diuretics, inhaled corticosteroids, or oral prednisone between groups No difference in parenteral report of chronic wheezing or cough between groups No difference in need for hospitalization between groups ADE: No ADE with AZM observed Developmental outcomes: No difference in death or moderate-to-severe NDI in AZM versus placebo group (47.2% versus 32.7%; p = 0.11) No difference BSID-III scores, ASQ-3 scores, or diagnosis of cerebral palsy between groups

ADE, adverse drug event; ASQ-3, Ages and Stages Questionnaire, third edition; AZM, azithromycin; BSID-III, Bayley Scales of Infant and Toddler Development, third edition; BW, birth weight; CA, corrected age; GA, gestational age; IV, intravenous; NDI, neurodevelopmental impairment

were performed and it was determined that serum concentrations rapidly decrease below the MIC_{50} of 1 mcg/mL within a few hours of a single 20 mg/kg dose. Therefore, a dosing regimen of 20 mg/kg/dose every 24 hours for 3 doses was simulated and azithromycin concentrations with this dosing strategy were predicted to remain above the MIC_{50} of 1 mcg/mL for 96 hours after the first dose.

Based on the simulation analysis from the previous study, Merchan et al[15] then evaluated a dose of 20 mg/kg IV every 24 hours for 3 days in 15 premature neonates. Six blood samples were obtained between 1 and 2, 2 and 4, 6 and 8, 25 and 48, 49 and 96, and 120 and 168 hours after first dose. Two tracheal aspirates, at least 2 hours apart, and 1 nasopharyngeal sample were obtained from intubated patients, and 2 nasopharyngeal samples, 2 hours apart, were obtained in non-intubated infants. Specimens were sent for culture and PCR assessment. Seven patients (47%) were culture and PCR positive for *Ureaplasma* prior to azithromycin treatment. After treatment, no patients had a positive *Ureaplasma* culture; however, 1 patient was PCR positive for *Ureasplasma* 4 to 5 days after the last dose. Four (26.7%) developed BPD, with a greater number of those being *Ureaplasma*-positive patients versus *Ureaplasma*-negative patients, 3 versus 1 (p = 0.28). The pharmacokinetic analysis portion of this study included data from 15 patients plus the data from their 2 previous single-dose pharmacokinetic studies.[13,14] For this study, the MIC_{50} and MIC_{90} were defined as 2 mcg/mL and 8 mcg/mL, respectively, which differed from their previous pharmacokinetic studies. Azithromycin 20 mg/kg IV every 24 hours for 3 doses resulted in a majority of observed plasma concentrations >2 mg/L for 120 hours after first dose. In addition, the authors noted that a 24-hour area under the curve (AUC_{24})/MIC_{90} for >4 hours would be effective for the eradication of *Ureaplasma*. Long-term pulmonary outcomes were assessed at 6 months corrected age for 6 *Ureaplasma*-positive and 8 *Ureaplasma*-negative patients. No differences were noted in number of respiratory hospitalizations, use of supplemental oxygen, visits for chronic cough or wheezing, or use of inhaled albuterol or steroids.

Long-Term Outcomes With Azithromycin. Only 1 study evaluated the long-term pulmonary and neurodevelopmental outcomes as the primary objective in preterm infants who received azithromycin for eradication of *Ureaplasma* (Table 4).[16] Viscardi et al[12] followed patients included in their initial prospective, placebo-controlled study to a corrected age of 22 to 26 months. The Tucson Children's Respiratory Study questionnaire, a validated tool to assess pulmonary complications, was completed by caregivers at a corrected age of 6, 12, and 22 to 26 months and

neurodevelopmental assessments (e.g., Gross Motor Function Classification System, Bayley Scales of Infant and Toddler Development, third edition [BSID-III], hearing and vision screening) were performed at 22 to 26 months of age. Pulmonary and neurodevelopmental assessments were performed for 86% and 87% of the 109 patients from the initial study[12] who had not died, respectively. For the primary study objective, there was no difference in the composite outcome of death or serious respiratory morbidity at a corrected age of 22 to 26 months between those who did and did not receive azithromycin, 34.8% versus 30.5% (p = 0.67). However, when specifically evaluating the 37 patients who tested positive for *Ureaplasma* (azithromycin, n = 16; placebo, n = 21), those that received azithromycin had a significantly higher incidence of serious respiratory morbidity versus those receiving placebo, 44.30% versus 15.2% (p = 0.036). There were also no significant differences in parenteral reports of chronic wheezing, hospitalization, or medication use between these patients. In addition, there was no significant difference in the composite outcome of death or moderate-to-severe neurodevelopmental impairment between those who did and did not receive azithromycin, 47.2% versus 32.7% (p = 0.11). There continued to be no significant difference for this composite outcome between treatment groups when evaluating the 18 patients receiving azithromycin and 22 patients receiving placebo who tested positive for *Ureaplasma*, 38.9% versus 40.9% (p = 0.99). A post hoc analysis revealed that patients with lower respiratory tract *Ureaplasma* colonization (i.e., tracheal aspirate positive) were discharged home and their supplemental oxygen was discontinued at a later PMA. These patients had a higher rate of death or serious respiratory morbidity at a corrected age of 22 to 26 months compared with tracheal aspirate–negative patients or patients that were never intubated (i.e., nasopharyngeal samples only).

Ballard et al[8] also assessed neurodevelopmental outcomes as a secondary objective for 69% of patients enrolled in the study. The mean ± SD corrected age at follow-up was 16.5 ± 5.2 months for azithromycin patients and 8.3 ± 5.4 months for placebo patients. There were no differences in BSID-II or Preschool Language Scale-4 scores between groups, with the exception of the azithromycin group having a higher Expressive Communication score on the Preschool Language Scale-4 (p = 0.03). Developmental outcomes were not assessed in any of the other studies included in this review.

Adverse Effects Associated with Azithromycin. Overall, most (88.9%) of the studies did not identify any adverse effects associated with the use of azithromycin compared with placebo.[8–11,13–16] Specifically, none of the studies noted development of pyloric stenosis or a QTc interval prolongation in any patient. Only 1 study noted a statistical difference in an adverse effect, with posthemorrhagic hydrocephalus occurring in 10% of patients receiving azithromycin compared with 0% of placebo (p = 0.01).[12] In addition, azithromycin was not associated with increased incidence of any morbidities or complications of prematurity. Two studies noted that feeding intolerance was significantly improved with azithromycin compared with placebo; this is likely due to the promotility effects associated with azithromycin.[8,12]

Discussion

Ureaplasma colonization affects approximately one third to one half of premature neonates who require respiratory support in the neonatal intensive care unit (NICU) and has been associated with an increased risk for negative neonatal outcomes.[4,9,11–15] Variability in the incidence of *Ureaplasma* in these studies is likely due to differences in patient populations (e.g., gestational age, respiratory support) and methods of testing (e.g., PCR, culture). *Ureaplasma* testing was performed in 7 (77.8%) of the studies.[8,9,11–15] Confirmation testing was performed using blood PCR (n = 1),[11] tracheal aspirate culture (n = 1),[8] tracheal aspirate and nasopharyngeal culture (n = 2),[13,14] tracheal aspirate PCR (n = 1),[9] and tracheal aspirate and nasopharyngeal culture and PCR (n = 2).[12,15] Azithromycin for *Ureaplasma* eradication and/or prevention of BPD has been evaluated in a total of 9 studies (n = 388), 5 of these being prospective, placebo-controlled clinical studies.[8–16] In addition to these 5 clinical studies,[8–12] there were 3 pharmacokinetic studies[13–15] that evaluated some clinical outcomes, and 1 follow-up study[8] focused on neurodevelopmental outcomes. It should be noted that several of these studies were conducted by the same research group and included some of the same patients. In most of these studies (88.9%), azithromycin was initiated prior to 72 hours of life, before birth infection status was known.[8–15] Patients were randomized and treated prior to their *Ureaplasma* infection status being known because of the delay in culture results or PCR results. Testing for *Ureaplasma* colonization at time of NICU admission is not routinely performed in many NICUs. A 2014 survey of 167 European NICUs identified that 47% of NICUs tested for *Ureaplasma* colonization at birth and these were most commonly obtained via endotracheal or nasopharyngeal sections with cultures and/or PCR tests performed on the samples.[6] At some institutions, *Ureaplasma* cultures or PCR tests may be send-out labs, which delays results and limits the ability to know the *Ureaplasma* status prior to initiation of azithromycin. Therefore, the design of these studies with the initiation of azithromycin when *Ureaplasma* status is unknown mimics what would likely be done in most NICUs.

The dosing used in these studies is variable and ranged from 5 to 20 mg/kg/day, and the duration ranged from 1 to 35 days. Most (66.7%) of the studies[11–16] evaluated the use of IV azithromycin only, whereas only 1 study[10]

(11.1%) evaluated the use of enteral azithromycin. For the remaining 2 studies (22.2%), IV azithromycin was initiated and changed to enteral when the patient reached full enteral feeds.[8,9] Initial doses used were extrapolated from dosing used for the treatment of pertussis, but there was concern that the 10 mg/kg/dose did not produce adequate serum drug concentrations for eradication of *Ureaplasma*.[13] The most recent prospective study used a dose of 20 mg/kg every 24 hours for 3 doses, which was based on the findings from the pharmacokinetic study of Merchan et al.[15]

Using the dosage regimen of 20 mg/kg every 24 hours for 3 doses, Viscardi et al[12] noted that *Ureaplasma* was eradicated in 100% of patients; however, eradication of *Ureaplasma* did not result in decreased incidence of BPD. There was no difference in the development of BPD between patients that received azithromycin versus placebo, even when specifically looking at the *Ureaplasma*-positive study patients.[12] This finding is similar to 5 previous studies that compared the development of BPD at PMA 36 weeks between those who received azithromycin versus placebo. Of these 6 studies, 5 found no statistical difference in BPD development when evaluating all patients enrolled.[8–12,16] Only 1 study noted a statistically significant lower incidence of BPD when specifically comparing *Ureaplasma*-positive patients treated with azithromycin compared with placebo ($p = 0.03$).[9] A recent meta-analysis that included 5 of the studies included in this review[8–12] showed no difference in risk for BPD in those that received azithromycin versus placebo (RR, 0.92; 95% CI, 0.71–1.19).[7] There continued to be no difference in risk for BPD when specifically evaluating the *Ureaplasma*-positive patients (RR 0.83; 95% CI, 0.66–1.03). Based on the studies included in this review, it does appear that azithromycin is effective in eradicating *Ureaplasma* from the respiratory tract; however, if using for the prevention of BPD, there does not appear to be adequate data to support use for this indication in the literature. Use of azithromycin also does not appear to have any long-term pulmonary or neurodevelopmental benefit when compared with placebo.

Based on the literature at this time, if azithromycin is used for eradication of *Ureaplasma*, a dose of 20 mg/kg IV every 24 hours for 3 days should be recommended. However, it should be noted that some experts believe that a more prolonged azithromycin course is needed to affect the development of BPD. There is a current randomized, placebo-controlled trial underway that is evaluating a 10-day course of azithromycin (20 mg/kg IV every 24 hours for 3 days, followed by 10 mg/kg IV every 24 hours for 7 days) in premature neonates born at <30 weeks' gestation in the first 72 hours of life.[17] The authors state that the first 3 days of treatment should adequately eradicate *Ureaplasma*, and the additional 7 days of treatment at a lower dose will be beneficial to prevent the rise of inflammatory mediators that typically occurs within 7 to 10 days of birth. The primary objective of this study is the combined outcome of moderate to severe chronic lung disease and mortality at PMA of 36 weeks. It will be interesting to see if this study demonstrates differences in rates of BPD due to differences in dosing and larger sample size (anticipated 789 patients) compared with the study by Viscardi et al.[12]

Overall, azithromycin appears to be well tolerated in the studies included in the review, because no patients developed pyloric stenosis or QTc interval prolongation. Azithromycin has been rated as a "known risk for prolongation of QTc-interval and Torsades de Pointes" in CredibleMeds based on reports in adult patients; however, there are no reports of QTc interval prolongation in neonates receiving doses similar to what has been evaluated in this review.[18] There is only 1 published case report of QTc interval prolongation and complete heart block in an infant that received an inadvertent overdose of 50 mg/kg IV.[19] Therefore, risk is low if azithromycin doses of 20 mg/kg are used in premature neonates; however, monitoring should still be recommended, specifically in patients who are receiving other agents associated with QTc interval prolongation. Erythromycin has been associated with 3 times greater risk for development of pyloric stenosis in neonates and infants up to 4 months of age in a recent meta-analysis (RR, 3.17; 95% CI, 2.38–4.23)[20]; however, there are limited reports with azithromycin. In a retrospective cohort study, Eberly et al[21] reported 8 times greater odds (aOR, 8.26; 95% CI, 2.62–26.0) for development of pyloric stenosis if term infants are exposed to azithromycin within the first 14 days of life, and nearly 3 times greater odds (aOR, 2.98; 95% CI, 1.24–7.20) if exposed between 14 and 42 days of life. Stark et al[22] noted an association with prematurity and development of pyloric stenosis, with 30% greater odds for development in premature patients. Therefore, monitoring of preterm patients for development of pyloric stenosis after receiving azithromycin for prevention of BPD or treatment of *Ureaplasma* should be recommended.

Conclusion

Based on the reviewed literature, azithromycin is effective for eradication of *Ureaplasma* in colonized neonates. However, azithromycin is not effective for prevention of BPD when used empirically in all very low birth weight premature neonates. Azithromycin may be beneficial for prevention of BPD when used in *Ureaplasma*-positive patients; however, selective administration to *Ureaplasma*-positive neonates may not be feasible because many NICUs do not perform testing in the institution's laboratory and results would be delayed. The most effective dose identified in the pharmacokinetic and clinical studies included in our review is 20 mg/kg/dose IV every 24 hours for 3 days. This dose achieved a 100% eradication rate, but it did not significantly decrease development of BPD at 36 weeks PMA.

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