



# Effects of Antenatal Azithromycin for *Ureaplasma* spp. on Neonatal Outcomes

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**Objective:** *Ureaplasma* spp. in the maternal genitourinary tract is increasingly known to cause preterm labor, spontaneous abortion, chorioamnionitis and adverse neonatal outcomes. However, controversies still remain regarding whether or not to treat it aggressively. The aim of this study was to evaluate the effects of antenatal azithromycin (AZ) for *Ureaplasma urealyticum* (UU) infection on neonatal complications in preterm infants.

**Methods:** Retrospective single-center case-control study of preterm babies delivered at <32 weeks' of gestation age (GA) between 2010 and 2014 were conducted. Cases were defined as infants with complete maternal AZ treatment when UU was confirmed and controls were without UU. Cases were matched with controls by birth year, GA, and birth weight. Subgroup analysis according to GA (23<sup>+0</sup>-28<sup>+6</sup> weeks' and 29<sup>+0</sup>-32<sup>+6</sup> weeks') were done as well.

**Results:** Of 169 cases identified 51 with untreated or incompletely treated mother, 26 died or transferred, and four with incomplete chart were excluded; thus 88 preterm infants were matched to 88 controls. Incidence of bronchopulmonary dysplasia (BPD) and early sepsis were same in both group; however, in very preterm infants between 23<sup>+0</sup> to 28<sup>+6</sup> weeks' GA, incidence of moderate-to-severe BPD was significantly higher in cases (42% vs. 16%,  $P=0.022$ ) and incidence of sepsis was significantly lower (8% vs. 26%,  $P=0.033$ ).

**Conclusion:** Maternal UU was associated with moderate-to-severe BPD even though AZ treatment was done. Early sepsis was significantly less developed with prenatal antibiotics at  $\leq 28$  weeks' GA. Hence selective antenatal azithromycin therapy of UU is still needed for improving neonatal outcomes.

**Key Words:** Cervical Cerclage, Cervical length measurement, Uterine cervical incompetence, Premature birth

## Introduction

*Ureaplasma urealyticum* (UU) is one of the frequently isolated microorganisms from the amniotic fluid and infected placentas.<sup>1,2</sup> Although UU is isolated from the vagina in 40% to 80% of sexually active asymptomatic women as a commensal organism, it can cause preterm delivery, spontaneous abortion or miscarriages, chorioamnionitis, neonatal morbidity, and/or perinatal death.<sup>3,4</sup> UU can be transmitted vertically from the mother to the fetus in utero, or to the newborn infant at delivery.<sup>5,6</sup>

Intrauterine UU infection is found to alter lung development, prolong inflammatory response and increase fibrotic reaction in animals.<sup>7</sup> In one study, the risk of moderate-to-severe bronchopulmonary dysplasia (BPD) development showed a 7.9-fold increase in mechanically ventilated infants being ventilated for any reason with positive UU tracheal aspirate,<sup>8</sup> and a two-fold increased risk for necrotizing enterocolitis (NEC) in preterm infants with respiratory UU infection.<sup>9</sup> UU colonization had been found in the blood, cerebrospinal fluid, and brain tissue and the risk of severe intraventricular hemorrhage was

increased to 2.5-fold higher in infants with positive serum UU colonization.<sup>10</sup>

Since genital mycoplasmas including UU are unable to produce cell walls, beta-lactams, vancomycin, sulfonamides, or trimethoprim is ineffective.<sup>2</sup> UU is generally susceptible to certain antibiotics that interfere with protein synthesis.<sup>2,11</sup> There are some studies that have evaluated the use of erythromycin in preterm infants with UU colonization and erythromycin was once known as a standard antibiotic for preterm premature rupture of membrane (PPROM) treatment.<sup>12-14</sup> Azithromycin (AZ) is an expanded-spectrum macrolide antibiotic that is supposed to have better tissue penetration than erythromycin; hence, it can be an alternative antibiotic.<sup>11,15</sup> Recent studies in rhesus monkeys suggested that antenatal multiple-dose AZ therapy could mitigate pregnancy-associated complications.<sup>16</sup> However, not many studies about the effectiveness of antenatal AZ treatment have been done, and whether or not AZ is effective is still being debated. Thus, the aim of this study was to demonstrate the clinical effects of antenatal AZ treatment of UU-colonized mothers on neonatal morbidity.

## Methods

### 1. Study subjects

All preterm infants who were admitted to Hallym University Medical Center between January 2010 and December 2014 were eligible for this study. Those without maternal UU results, those who were transferred to or from other institutes for any reason, those without complete medical charts, or those who died before 28 days of life were excluded. The final included infants were those born at  $\leq 32$  weeks' of gestational age (GA), since most of the near-term infants who were considered for inclusion did not need intensive care. Then infants with complete antenatal AZ treatment of UU-colonized mothers (cases) were matched with controls by birth year, GA, and birth weight ( $\pm 100$  g). This retrospective single-center case-control study was approved by the institutional review boards of our facility.

### 2. Urealyticum confirmation and azithromycin treatment

UU samples from the maternal lower genitalia area were ob-

tained from those who were admitted for any reason, via by vaginal swabs during a physical examination. MYCOFAST<sup>®</sup> Evolution 2 (International Microbio, Signes, France) was used for culture analysis, and polymerase chain reaction (PCR) was done as well. If the interval between admission and delivery was more than one week, the microbiological examinations were repeated. To obtain a sufficient amount of sample, all of the procedures were performed twice. UU-positive was defined as with at least one result was being positive, and then AZ was administrated for treatment. Complete antenatal azithromycin therapy was defined when oral AZ of 500 mg/day was administrated for three consecutive days before delivery.

### 3. Definitions of parameters

The maternal and clinical variables compared between the cases and controls were GA, birth weight, preterm labor, PPRM, antenatal steroid administration, chorioamnionitis, surfactant use, BPD, patent ductus arteriosus (PDA), retinopathy of prematurity (ROP), early sepsis, NEC, and cranial sonography abnormality.

PPROM was defined as the rupture of membranes  $\geq 24$  hours before delivery. Clinical chorioamnionitis was identified in the mother with fever ( $\geq 37.8^\circ\text{C}$ ) and two or more of the following: leukocytosis ( $\geq 15,000 \mu\text{L}$ ), elevated C-reactive protein ( $\geq 3 \text{ mg/L}$ ), foul odor, maternal tachycardia ( $>100$  beats/minute), and/or fetal tachycardia ( $>160$  beats/minute). Histological chorioamnionitis (HC) was defined as a placenta with polymorphonuclear leucocyte infiltration, as confirmed by a pathologist.

Surfactant was used prophylactically when the infants were at less than 30 weeks' gestation or curatively when respiratory distress syndrome was diagnosed. Early sepsis was diagnosed on the basis of a positive blood culture, along with any one of the known clinical signs demonstrated less than three days after birth. PDA with treatment was defined as PDA with medical treatment and/or surgical operation following confirmation by echocardiography. NEC was diagnosed using modified Bell's criteria and  $\geq$  stage IIA was analyzed. BPD was diagnosed as oxygen dependency at 36 weeks of post-menstrual age according to the National Institutes of Health consensus definition and severity was classified as mild, moderate, or severe.<sup>17</sup> Abnormal sonography was defined as intraventricular hemorrhage ( $\geq$  grade 3)  $\pm$  periventricular leukomalacia.

#### 4. Data analysis

Statistical analysis was performed using Student's *t*-test for normally distributed data and the chi-squared test or Fisher's exact test for comparisons between frequencies. All statistical analysis was performed with SPSS (version 22, IBM, Armonk, NY, USA). Data were reported in the format of mean±standard deviation or number (%). Statistical significance was accepted at  $P<0.05$ .

## Results

### 1. Overall characteristics of study population

During the study period, 169 preterm infants of  $\leq 32$  weeks' GA were diagnosed as having maternal UU colonization. Of then, 51 cases were excluded due to incomplete or untreated mother at first. Of the remaining 118 cases 26 died or transferred during their neonatal hospitalization and another four had to be excluded due to incomplete chart. From the cohort of 26 mothers, four were transferred to a different department (two for PDA surgery and two for treatment of hydrocephalus). From the final cohort of 22 mothers, 10 were in control group and 12 were in UU+ group. Causes of deaths were respiratory disease (nine patients, 41%), GI-related disease (one patients, 5%), sepsis (four patients, 18%), multiple organ failure (six patients, 27%), and cerebral hemorrhage (two patients, 9%). No deaths from UU infection have been confirmed. Thus the study population comprised 88 cases and 88 matched controls.

The demographics and clinical characteristics of cases and controls are depicted in Table 1. There were no significant differences regarding primipara, PPRM, preterm labor, antenatal steroids, and chorioamnionitis between cases and controls of maternal variables. HC which was confirmed by pathologist after delivery showed no difference between two groups. For neonatal characteristics between cases and control, we found no significant differences between Apgar scores at 1 minute and 5 minutes, length of stay, duration of use of ventilation, and duration of oxygen supplement (Table 1).

### 2. Neonatal morbidities according to the gestational age at birth

There were no significant differences in the incidence of

**Table 1.** The Demographics and Clinical Characteristics of Study Population

	Cases (n=88)	Controls (n=88)	P- value
Gestational age (wks)	28.8±2.3	28.8±2.3	1.000
Birth weight (g)	1,349.5±402.5	1,321.9±381.8	0.641
Apgar score at 1 minute	3.9±2.0	4.0±1.8	0.720
Apgar score at 5 minute	6.1±1.7	6.1±1.8	1.000
Length of stay (days)	60.5±30.1	61.2±29.3	0.873
Duration of use of ventilation (days)	11.8±18.5	15.4±27.1	0.298
Duration of oxygen supplement (days)	25.6±32.8	26.3±34.7	0.892
Primipara (%)	20 (22.7)	29 (33.0)	0.178
PPROM (%)	42 (47.7)	38 (43.2)	0.545
Preterm labor (%)	76 (86.4)	68 (77.3)	0.171
Antenatal steroids (%)	80 (90.9)	77 (87.5)	0.466
Chorioamnionitis			
Clinical (%)	41 (46.6)	38 (43.2)	0.649
Histologic (%)	35 (50.0)	30 (49.2)	0.925

Values presented as mean±standard deviation or n (%).

Abbreviation: PROM, preterm premature rupture of membrane.

surfactant use (56% vs. 60%,  $P=0.541$ ) and BPD (35% vs. 43%,  $P=0.280$ ). Other parameters including PDA with treatment, ROP with laser, NEC, early sepsis, abnormal cranial sonography showed no significant differences as well. Significant difference was found regarding higher incidence of moderate-to-severe BPD in cases (18% vs. 7%,  $P=0.038$ ) (Table 2).

Since gestational and/or birth weight is one of the major factors for neonatal morbidities, we divided the study populations into subgroups regarding GA; specifically, infants with 29<sup>+0</sup>–32<sup>+6</sup> weeks' GA (cases n=50 vs. controls n=50, respectively) and infants with 23<sup>+0</sup>–28<sup>+6</sup> weeks' GA (cases n=38 vs. controls n=38, respectively). In a subgroup analysis, no significant differences were shown with respect to surfactant use, BPD, PDA with treatment, ROP with laser, NEC, and cranial sonography abnormality between cases and controls. None of the infants with  $\geq 29$  weeks' GA had moderate-to-severe BPD and ROP with laser.

In infants of 23<sup>+0</sup>–28<sup>+6</sup> weeks' GA, the incidence of moderate-to-severe BPD was higher in cases (42%) than in controls (16%) ( $P=0.022$ ) and the incidence of early sepsis was significantly lower in cases (8%) than in controls (26%) ( $P=0.033$ ).

**Table 2.** Comparison of Neonatal Morbidities between Infants with Antenatal Azithromycin Treated Group and Antenatal UU-Negative Groups

	Cases (n=88)	Controls (n=88)	P- value
Surfactant use	49 (55.7)	53 (60.2)	0.541
29 <sup>+0</sup> -32 <sup>+6</sup> week	14 (28.0)	16 (32.0)	0.828
23 <sup>+0</sup> -28 <sup>+6</sup> week	35 (92.1)	37 (97.4)	0.304
BPD	31 (35.2)	38 (43.2)	0.280
29 <sup>+0</sup> -32 <sup>+6</sup> week	2 (4.0)	7 (14.0)	0.160
23 <sup>+0</sup> -28 <sup>+6</sup> week	29 (76.3)	31 (81.6)	0.779
Moderate-to-severe BPD	16 (18.2)	6 (6.8)	0.038
29 <sup>+0</sup> -32 <sup>+6</sup> week	0	0	
23 <sup>+0</sup> -28 <sup>+6</sup> week	16 (42.1)	6 (15.8)	0.022
PDA with medication±operation	11 (12.5)	17 (19.3)	0.303
29 <sup>+0</sup> -32 <sup>+6</sup> week	1 (2.0)	2 (4.0)	1.000
23 <sup>+0</sup> -28 <sup>+6</sup> week	10 (26.3)	15 (39.5)	0.329
ROP with laser treatment	12 (13.6)	14 (16.3)	0.675
29 <sup>+0</sup> -32 <sup>+6</sup> week	0	0	
23 <sup>+0</sup> -28 <sup>+6</sup> week	12 (31.6)	14 (36.8)	0.809
NEC (≥stage IIA)	4 (4.5)	1 (1.1)	0.368
29 <sup>+0</sup> -32 <sup>+6</sup> week	1 (2.0)	0	1.000
23 <sup>+0</sup> -28 <sup>+6</sup> week	3 (7.9)	1 (2.6)	0.615
Early sepsis	8 (9.1)	13 (14.8)	0.353
29 <sup>+0</sup> -32 <sup>+6</sup> week	5 (10.0)	3 (6.0)	0.715
23 <sup>+0</sup> -28 <sup>+6</sup> week	3 (7.9)	10 (26.3)	0.033
IVH (≥grade 3)±PVL	6 (6.8)	10 (11.4)	0.432
29 <sup>+0</sup> -32 <sup>+6</sup> week	1 (2.0)	3 (6.0)	0.617
23 <sup>+0</sup> -28 <sup>+6</sup> week	5 (13.2)	7 (18.4)	0.754

Values are presented as number (%).

Abbreviations: UU, *Ureaplasma urealyticum*; BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.

## Discussion

The subjects were initially divided into three groups: UUTx (UU+ mothers who received antenatal azithromycin therapy, n=88), UUNOTx (UU+ mothers who did not receive antenatal azithromycin therapy, n=51), and control group. However, since this study was a retrospective study and we wanted to evaluate the effect of AZ, we excluded those who did not receive or received incomplete antenatal azithromycin therapy (UUNOTx group) in the end. In this retrospective single-center case-control study, we demonstrated that maternal UU colonization

was significantly associated with moderate-to-severe BPD despite antenatal AZ treatment.

Many studies demonstrated that the isolation of UU from the placenta or the lower genital tract during pregnancy plays a causal role in the process of intrauterine inflammation and infection-driven preterm labor.<sup>10,18,19</sup> Hence, as Acosta et al.<sup>16</sup> said, preterm delivery caused by intrauterine infection can be potentially “preventable” and that maternal antibiotics could be administered to prevent and treat intrauterine infection. Their study on non-human primates showed that repeated IV doses of maternal AZ could be accumulated sufficient enough to clear *Ureaplasma parvum* (*U. parvum*) from the amniotic fluid. Another study in an ovine model by Miura et al.<sup>19</sup> also showed that maternal antenatal azithromycin therapy of either IV only or IV+ intra-amniotic AZ effectively eradicated macrolide-sensitive *U. parvum* from the amniotic fluid. However, in our study, there was no significant differences in the incidence of preterm labor between two groups (86% vs. 77%,  $P=0.171$ ). This finding might explain the ineffectiveness of antenatal treatment of AZ and further investigations are needed.

Meanwhile, the frequency of perinatal transmission such as vertical transmission or intrauterine infection from UU-colonized mothers was reported to be 58% for preterm infants<sup>9</sup> and 22% to 55% for full-term infants.<sup>20</sup> UU isolation in the preterm respiratory tract was associated with neonatal pneumonia, severe respiratory failure, and BPD.<sup>16</sup> Since three independent groups first reported the association between lower respiratory tract UU colonization in very preterm infants and the development of chronic lung disease in 1988, numerous studies about UU colonization and BPD have been documented with different results.<sup>4,21,22</sup> One study by Sung et al.<sup>8</sup> demonstrated that the risk of the development of moderate-to-severe BPD showed a 7.9-fold increased risk in mechanically ventilated infants with a positive tracheal aspiration, as compared with mechanically ventilated infants with a positive nasopharyngeal sample alone. The associations between respiratory tract UU colonization and BPD have been confirmed by many studies, even though gestational age appeared to be a major confounder.<sup>23-25</sup>

Recently, studies about the effects of macrolide antibiotics including erythromycin and/or AZ given either prophylactically or therapeutically to reduce BPD or other neonatal morbidities are reported with different results.<sup>7,12,26</sup> A systematic review

with meta-analysis showed promising results of prophylactic AZ therapy in terms of a significant reduction in BPD,<sup>7</sup> while a very recent case-control study demonstrated no significant therapeutic effect of erythromycin on pulmonary short- and long-term morbidity.<sup>27</sup> Nevertheless, studies about antenatal macrolide treatment on neonatal morbidities are sparse. In our study about antenatal AZ treatment, it showed that overall BPD incidence seemed to be similar between cases and controls; however, there was no effect on reducing the development of moderate-to-severe BPD in certain gestational age ranges. Hence, the administration of single antibiotics to eradicate intrauterine infection may not be sufficient as other studies have reported, and additional anti-inflammatory therapy or selective treatments might be needed.<sup>19,28,29</sup> Risk factors of BPD include not only sepsis, but also RDS, pulmonary interstitial emphysema, short gestational period, patent ductus arteriosus, increased pulmonary arterial pressure, and high peak inspiratory pressure. Several studies reported that UU infection causes bronchopulmonary dysplasia in premature babies. One of the hypotheses state that phospholipase A2 produced by UU suppresses the production of pulmonary surfactant.<sup>30,31</sup> More detailed mechanism discovered hitherto explains that the generation of bronchopulmonary dysplasia is due to an increased secretion of proinflammatory cytokines (such as IL-6 and TNF- $\alpha$ ) by phagocytes when UU colony formation occurs.<sup>32</sup> In this study, within mild BPD patients, the prevalence of bronchopulmonary dysplasia between the UU infection group (treated) and the control group was not significantly different. On the other hand, moderate and severe BPD group showed higher prevalence of bronchopulmonary dysplasia in mothers with less gestational age from the UU infection group. We have previously mentioned as the limitation of our study that Az treatment may be an insufficient stand alone treatment as mentioned in other studies. This allows us to speculate that additional anti-inflammatory or selective treatments are needed. Furthermore, in the group of premature babies with very short gestational age, normal lung development is even more difficult. The babies are put into the environment with continuous damage against alveolarization from lengthened ventilation and oxygen therapies. In addition, the babies are affected by UU infection from the mothers. Together, the prevalence is significantly higher in severe BPD group compared to the control group.

In our findings, one unique result was that the incidence of early sepsis was significantly low with antenatal AZ treatment in infants of sepsis was' GA (8% vs. 26%,  $P=0.033$ ) although the total incidence of early sepsis in preterm babies  $\leq 32$  weeks' GA between cases and controls were similar (9% vs. 15%,  $P=0.353$ ). In general, infected amniotic fluid and placenta from UU infected mother can infect the newborn.<sup>5,33</sup> This vertical infection can cause sepsis in the newborn, and infected amniotic fluid also allows potential congenital pneumonia, sepsis from systemic infection, and CNS infection.<sup>34</sup> If the newborn is likely to be premature due to UU infection, he or she is more prone to sepsis caused by other bacteria. This is because premature babies have suppressed immune system and mucosal barrier function, and therefore are more prone to infection. Sepsis has multiple risk factors including low birth weight, maternal infection, chorioamnionitis, premature rupture of membranes, and fetal hypoxia.<sup>22</sup> However, the fact that premature babies less than 28-week-old from mothers who received Az treatment had significantly lower prevalence of early sepsis compared to the other groups indicate potential effects of antenatal UU treatment. Waites et al.<sup>35</sup> described that even though infection in the bloodstream of neonates had not been documented, there were the potential ability of UU to produce invasive disease. Since studies about the effects of antenatal AZ on early sepsis are rare, our results could suggest a promising way to reduce early sepsis in preterm infants.

There are number of limitation in our study. First, variable antenatal antibiotics other than AZ were used, and we could not control for them since this was a retrospective study. However, this study was a single center study; hence, similar antibiotics were used for study populations apart from AZ. Second, a follow-up UU culture and/or PCR were not implemented to confirm UU-negative conversion. Hence, a large scaled randomized control study is urgently needed to prove these study results. Thirdly, although late-onset sepsis is known as one of the risk factors of BPD, it was not considered in our study. Currently, our center is performing the examinations of premature babies (under 35 weeks) with consent from their parents. Sample collection is done through nasopharynx if the baby has no intubation or trachea and nasopharynx if the baby has intubation. However, in the process of obtaining the consent from the parents, several of them have refused to provide the

consent. This led to insufficient number of samples for the power of the study. In order to assess the effects of antenatal AZ treatment in the mothers on premature births—which is the main question of the study—we have performed in–depth follow–up of UU condition in the premature babies. We had to collect more data in order to perform multivariate analysis considering the effects between groups when UU was negative and when UU was positive by detailing follow–up of UU condition in the premature babies. With the data we have collected thus far, we could not deduce any significant result. Additional data needs to be collected in future, and we plan on addressing this issue as a main question of our next study.

Furthermore, the limitation of this study is the lack of comparative analysis of neonatal complications in the premature babies between the two subgroups of mothers: the group of UU negative mothers in the re–examination after antenatal Az treatment, and the group of UU positive mothers in the re–examination.

In addition to all premature babies born between 23<sup>+0</sup>–28<sup>+6</sup> week were given oxygen and ventilator treatment, and premature babies born between 29<sup>+0</sup>–32<sup>+6</sup> week were given ventilator treatment with varying ventilation therapies for different babies. It is difficult to create subgroups as the therapies (such as high frequency ventilation, positive pressure–limited, time cycle method, nasal continuous positive airway pressure, high flow nasal cannula, and etc.) change frequently according to the conditions and weaning stages of the babies. One possible assessment is to use the first ventilation therapy after the birth as the sole variable, create subgroups, and perform multiple regression analysis in order to assess whether or not UU affects the severity of BPD. However, due to the limited number of cases, this issue should be addressed in the future.

In conclusion, maternal UU colonization was associated with the development of BPD, especially moderate–to–severe BPD, even though antenatal AZ treatment was done. Early sepsis was significantly less developed with the administration of antenatal antibiotics in ially mod' GA. Hence, selective antenatal azithromycin therapy of UU is still needed for improving neonatal outcomes.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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