

The Value of *Ureaplasma urealyticum* Tracheal Culture and Treatment in Premature Infants Following an Acute Respiratory Deterioration

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OBJECTIVE:

To determine if treatment of *Ureaplasma urealyticum* (Uu), found at the time of an acute respiratory deterioration, decreases the incidence of chronic lung disease (CLD) in very low birth weight infants (VLBW).

STUDY DESIGN:

Between 1996 and 1999, medical records of all mechanically ventilated VLBW infants, who had an acute respiratory deterioration, were reviewed for gestational age (GA), birth weight (BW), gender, presence of CLD, Uu tracheal cultures, and erythromycin treatment.

RESULTS:

A total of 100 patients met our inclusion criteria (GA: 26.2 ± 1.7 weeks, BW: 737 ± 167.1 g (mean \pm SD)). Uu was present in 46.3% (38/82) of patients with CLD versus 50% (9/18) of patients without CLD (odds ratio 0.86 (CI: 0.31 to 2.39); $p = 0.77$). Erythromycin treatment was not found to be protective against the development of CLD (odds ratio: 1.46 (CI: 0.25 to 8.31); $p = 0.66$).

CONCLUSION:

Following an acute respiratory deterioration, tracheal isolation, and treatment of Uu may not decrease the incidence of CLD in VLBW infants.

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INTRODUCTION

Ureaplasma urealyticum (Uu) is a common pathogen of the vaginal flora during pregnancy.¹ Uu transmission from mothers to

their infants is more common in premature (8.5%) than in full-term babies (0.9%).² In very low birth weight infants (VLBW), some investigators have shown an association between Uu tracheal colonization and acute respiratory failure, chronic lung disease (CLD),³ and death,⁴ whereas others have failed to show an association.⁵ It has been suggested that treatment of infants colonized with Uu may prevent the development of CLD.⁶ However, treatment of colonized infants remains controversial especially when erythromycin use in newborns is associated with significant morbidity,^{5,7} and several studies have shown that treatment of all infants with Uu colonization does not decrease the incidence of CLD.^{5,8,9} Uu cultures are often obtained by clinicians when infants undergo acute respiratory deterioration. Positive results then prompt treatment in the hope of reducing short- and long-term respiratory complications. Treatment of infants when Uu is discovered at the time of an acute respiratory deterioration has not been studied.

The objective of this study was to determine if treatment of Uu, during an acute respiratory deterioration, decreases the incidence of CLD in ventilated VLBW infants.

MATERIALS AND METHODS

Patients

Medical records of all VLBW premature infants (<1500 g) who were admitted to the Neonatal Intensive care unit between 1996 and 1999 were reviewed. All VLBW infants who were intubated and mechanically ventilated for ≥ 2 weeks, and who had tracheal secretions cultured for Uu following an acute respiratory deterioration were included for this study. An acute respiratory deterioration was defined as multiple oxygen desaturations (a pulse oximetry <93%) requiring an increase in the fraction of inspired oxygen (FiO₂) to >50% or an increase in ventilatory support. Further an increase in ventilatory support was defined as an increase by at least 1 cm of H₂O of the peak inspiratory pressure (PiP), or positive end expiratory pressure (PEEP), or mean airway pressure (MAP) or an increase in the ventilator rate by at least 5 breaths/min. Patients were excluded if they had a severe congenital abnormality or were extubated within the first 2 weeks of life. Patients who were intubated without evidence of an acute respiratory deterioration, or who had acute respiratory deterioration secondary to a reversible mechanical problem such as self-

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extubation, inappropriate endotracheal tube position, endotracheal tube obstruction (from secretion plugs) were also excluded.

Medical records were reviewed for gestational age (GA), birth weight (BW), gender, the presence of CLD (defined as requirement for oxygen supplementation at 36 weeks of corrected GA), presence of Uu, and use of erythromycin (for the treatment of ureaplasma). Risk factors reported to be associated with CLD were also reviewed including: premature rupture of membranes (PROM), days of mechanical ventilation, postnatal use of steroids, presence of a patent ductus arteriosus (PDA, confirmed by echocardiography and treated if symptomatic), and sepsis (confirmed by a positive blood culture).

Statistical Analysis

For interval level data, the *t*-test was used. The Mann–Whitney *U*-test was used for nonparametric interval data. Interval level data were reported as the mean \pm SD. Statistical significance was defined a priori as a *p*-value <0.05 , two-tail.

For nominal data, the χ^2 test was used for large groups and the Fisher's exact test was used for small groups. An odds ratio analysis was also performed using the 95% confidence interval.

To adjust for possible confounding, a logistic regression analysis was used. Variables known to be associated with CLD were entered in a logistic regression model using the presence or absence of CLD as a classifying and dependent variable.

RESULTS

During the study period, 510 VLBW infants were admitted to the NICU. A total of 401 infants required intubation and mechanical ventilation, but only 185 premature babies remained intubated and ventilated for ≥ 2 weeks. Of the 185, 15 infants died. From the remaining 170 patients, 119 patients had an acute respiratory deterioration and met our inclusion criteria, but only 84% (100/119) had tracheal cultures for Uu available to review for the study.

Among patients who had available Uu cultures, there was no difference between infants who developed CLD and those who did not develop CLD regarding their gender, race, and presence of PROM, sepsis, Uu, or PDA. However, infants who developed CLD had a smaller GA and BW, longer NICU stay, and remained intubated and mechanically ventilated for a longer period of time (Table 1). The incidence of CLD did not differ between patients who did or did not have cultures available to review for the study (82% (82/100) versus 68.4% (13/19) respectively, *p* = 0.29).

When patients with Uu were compared to patients without Uu, the incidence of CLD did not differ between the two groups (81% (38/47) versus 83% (44/53) respectively; *p* = 0.98). There was also no difference between the two groups regarding GA, gender, race, BW, incidence of PROM, or the time when Uu cultures were obtained (18.6 \pm 13.4 days (range: 4 to 59) for culture positive patients versus 16.9 \pm 14.1 days (range: 3 to 72) for culture negative patients). Days of ventilation, use of postnatal steroids, sepsis, and NICU length of stay also did not differ between the two groups. However, patients with Uu had a lower incidence of PDA in comparison to those without Uu (51% (24/47) versus 81.1% (43/53), respectively; *p* = 0.003), but among all patients with PDA, the incidence of CLD was similar between infants with or without Uu (83.3% (20/24) versus 86.0% (37/43) respectively, *p* = 0.67).

Among all Uu-positive patients, infants who developed CLD were similar to those who did not regarding GA, gender, race, BW, incidence of PROM, sepsis, use of erythromycin treatment for Uu, and incidence of PDA. However, infants who developed CLD remained mechanically ventilated longer and received more steroids (Table 2). After adjustment for risk factors associated with CLD, mechanical ventilation was found to be the only statistically significant factor associated with CLD in patients with Uu. Whereas, the other independent factors such as GA, BW, race, presence of a PDA, sepsis, and use of erythromycin were not found to be associated with CLD in this group of patients (Table 3).

To determine if treatment of Uu with erythromycin had an effect on the development of CLD, a comparison was made between

Table 1 Patients Cultured for Uu Following an Acute Respiratory Deterioration

	Presence of CLD* (<i>n</i> =82)	Absence of CLD* (<i>n</i> =18)	Odds ratio (95% CI)	<i>p</i> -Value
GA < 28 weeks (%)	67/82 (81.7)	11/18 (61.1)	2.84 (0.94–8.54)	0.057
Gender (% male)	41/82 (50)	10/18 (55.55)	0.80 (0.28–2.23)	0.67
Race (% white)	31/82 (37.8)	8/18 (44.4)	0.75 (0.27–2.13)	0.60
BW \leq 750 g	55/82 (67.07)	6/18 (33.33)	4.07 (1.37–12.03)	<0.01
PROM [†] (%)	6/82 (7.31)	0/18 (0)	3.14 (0.16–58.34)	0.23
Sepsis (%)	18/82 (21.95)	2/18 (11.1)	2.25 (0.47–10.70)	0.30
Ureaplasma (%)	38/82 (46.34)	9/18 (50)	0.86 (0.31–2.39)	0.77
PDA [‡] (%)	57/82 (69.51)	10/18 (55.55)	1.82 (0.64–5.16)	0.25
Ventilation \geq 30 days (%)	5/18 (27.77)	60/82 (73.17)	7.09 (2.26–22.19)	<0.01
Postnatal steroids (%)	75/82 (91.46)	10/18 (55.5)	8.57 (2.55–28.74)	<0.01
NICU [§] stay \geq 60 days (%)	54/82 (65.85)	6/18 (33.33)	3.85 (1.30–11.37)	0.01

*CLD: chronic lung disease; [†]PROM: premature rupture of membranes; [‡]PDA: patent ductus arteriosus; [§]NICU: neonatal intensive care unit.

Table 2 Patients With Positive Uu Cultures

	Presence of CLD* (n=38)	Absence of CLD* (n=9)	Odds ratio (95% CI)	p-Value
GA < 28 weeks	31/38 (81.57)	5/9 (55.55)	3.54 (0.75–16.68)	0.10
Gender (% male)	20/38 (52.63)	6/9 (66.66)	0.55 (0.12–2.55)	0.45
Race (% white)	14/38 (36.84)	1/9 (11.11)	4.66 (0.52–41.31)	0.14
BW ≤ 750 g	26/38 (68.42)	4/9 (44.44)	2.70 (0.61–11.92)	0.18
PROM [†] (%)	4/38 (10.52)	0/9 (0)	2.47 (0.12–50.21)	0.31
Sepsis (%)	6/38 (15.78)	1/9 (11.1)	1.50 (0.15–14.29)	0.72
Erythromycin	31/38 (81.57)	7/9 (77.77)	1.26 (0.21–7.44)	0.79
PDA [‡] (%)	20/38 (52.63)	4/9 (44.44)	1.38 (0.32–5.98)	0.66
Ventilation ≥ 30 days (%)	29/38 (76.31)	2/9 (22.22)	11.27 (1.97–64.27)	<0.01
Postnatal steroids (%)	33/38 (86.84)	3/9 (33.33)	13.2 (2.47–70.46)	<0.01
NICU [§] stay ≥ 60 days (%)	24/38 (63.15)	3/9 (33.33)	3.42 (0.73–15.90)	0.10

See footnotes in Table 1.

Table 3 Adjusted Odds Ratio of Risk Factors Associated With CLD in Infants With Uu-positive Tracheal Cultures

	Adjusted odds ratio	Confidence interval	p-Values
GA ≤ 27 weeks	2.20	0.36–13.20	0.387
BW ≤ 750 g	2.29	0.45–1.67	0.315
Race (white)	4.01	0.61–26.19	0.146
Ventilation ≥ 30 days	20.77	2.88–149.73	0.002
PDA	0.17	0.02–1.50	0.112
Sepsis	0.86	0.10–6.87	0.889
Erythromycin	1.46	0.25–8.31	0.664

treated (38/47) and untreated (9/47) patients. The incidence of CLD did not differ between the two groups (81.6% (31/38) for the treated versus 77.8% (7/9) for the untreated group; $p = 0.79$). The two groups were similar regarding their gender, race, incidence of PROM, days of ventilation, use of postnatal steroids, PDA, sepsis, and NICU length of stay; however, they were different regarding BW and GA. Infants who were treated with erythromycin were less premature (26.4 ± 1.7 weeks for the treated versus 25.8 ± 1.5 weeks for the untreated group; $p = 0.053$) and heavier at birth (778.2 ± 197.1 g for the treated versus 674 ± 92.6 g for the untreated group; $p = 0.003$). Treated infants received erythromycin, on average, at the age of 20.4 ± 11.7 days (range: 9 to 65 days) for the duration of 13.5 ± 2.2 days (range: 7 to 19 days).

DISCUSSION

This study demonstrates that the isolation of Uu from the trachea of VLBW infants following an acute respiratory deterioration at 2 weeks of age is not a risk factor for the development of CLD. Furthermore, treatment of Uu-positive infants following such a respiratory deterioration does not affect the respiratory outcome of these VLBW infants.

Several studies have shown an association between Uu and development of CLD in premature infants, whereas others have failed to demonstrate an association. In a metaanalysis, Wang et al.³ have shown an association between Uu colonization and CLD in premature infants (with a relative risk of 1.72). In a study of infants less than 31 weeks GA, Iles et al.¹⁰ have also shown an association between Uu and CLD (87% of Uu-positive versus 41% Uu-negative patients developed CLD at 36 weeks GA). In our study, the incidence of CLD (at 36 weeks GA) could not be determined between Uu-positive and Uu-negative patients because only intubated patients following an acute respiratory deterioration were cultured, whereas in other studies all infants were cultured for Uu. Therefore, our data do not reflect the true incidence of CLD among infants colonized with Uu. For the same reason, the data in this study also cannot be used to determine whether colonization with Uu is associated with subsequent CLD. A large percentage of infants did not have cultures performed, and that group contained additional infants without CLD.

The incidence of CLD was not different among patients who were cultured or uncultured for Uu following an acute respiratory deterioration in our study, suggesting that the presence of Uu in the group of patients who were cultured might have been a colonization rather than an infection. It is difficult to determine if the isolation of Uu in the tracheal secretion was a pure colonization or an infection from our retrospective review. Many investigators have not found a relationship between Uu colonization and development of respiratory disease. Da Silva et al.¹¹ in a prospective study of 108 VLBW infants found that Uu was frequently detected in the airways of premature infants, but its presence was not associated with the development of CLD, duration of ventilation, oxygen dependency and length of hospital stay. Saxen et al.¹² found no significant role of Uu airway colonization in the development of CLD in a Finnish population of 49 preterm infants (less than 30 weeks GA). Bowman et al.¹³ in a prospective cohort study of 124 premature infants weighing less than 1000 g at

birth found also no differences in CLD, duration of oxygenation, or length of stay between colonized and noncolonized infants with Uu. Heggie et al.⁵ in their study of 224 VLBW infants found no differences in outcome between Uu-positive and Uu-negative premature infants. The incidence of CLD (at 36 weeks corrected GA) in Heggie's Uu-positive population was similar to our population (around 80%). The similarity between our results and theirs could have been due to the similarity in the studied populations (on average 26 weeks GA), or the timing of erythromycin treatment (at 2 weeks of age). In our study, tracheal aspirates were not obtained from all VLBW infants. Our results reflect the selection of critically ill patients for Uu screening; patients who were screened for Uu had an acute respiratory deterioration. Treatment with erythromycin was not controlled or randomized, the decision to treat or not to treat was made by the attending neonatologist rather than by random selection. It is possible that infants selected for erythromycin treatment were more seriously ill than infants who were not treated, and that erythromycin prevented the development of an adverse respiratory outcome.

In order to determine whether Uu has a causative role in the development of CLD, several authors have studied the effect of erythromycin on the respiratory outcome of premature infants with Uu. In a prospective study, Lyon et al.⁸ found that Uu isolation was associated with tracheal inflammatory responses, but erythromycin treatment was not associated with a reduction in the incidence or severity of CLD at 36 weeks GA. In another randomized controlled study, Jonsson et al.⁹ found that erythromycin treatment reduced Uu colonization but did not alter the duration of oxygen supplementation in premature infants. In our study, we looked at a subpopulation of patients that had Uu in the presence of acute respiratory deterioration. Even in this group, erythromycin did not decrease the incidence of CLD in Uu-positive patients. Treatment of Uu at 2 weeks of age (on average) may have been too late to prevent CLD. The development of CLD may already be inevitable that time due to the duration of mechanical ventilation regardless of the presence or absence of Uu or to other confounding etiologies. The data were adjusted in our logistic regression analysis for confounding variables such as presence of a PDA in general, but not for a symptomatic PDA at the time of the respiratory deterioration. A large prospective, controlled, randomized study is needed in the future to determine if early intervention and treatment (within the first days of life) of premature infants exposed to Uu in utero prevents the development of CLD.

We conclude that, following an acute respiratory deterioration, tracheal isolation and treatment of Uu at 2 weeks of age may not

alter the respiratory outcome of critically ill VLBW infants already at high risk for the development of CLD.

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