



Ureaplasma Urealyticum and Mycoplasma Hominis Colonization and Chronic Lung Disease in Preterm Neonates Under Ventilation

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ABSTRACT

Background: Ureaplasma urealyticum (U. urealyticum) and Mycoplasma hominis (M. hominis) are two important pathogens in neonatal respiratory tract infections. As low gestational age and birth weight increase the colonization rate with these pathogens, and they are also risk factors of chronic lung disease (CLD), it is difficult to establish a statistically significant relation between these two factors.

Objectives: To determine the colonization rate of preterm ventilated neonates with U. urealyticum and M. hominis, and the relationship between infection and chronic lung disease in these neonates, a prospective study was performed.

Patients and Methods: Determining tracheal colonization rate of preterm neonates with ureaplasma and mycoplasma and its relation to CLD. In a cohort prospective study in Hazrat Rasoul Akram Hospital, with 62 ventilated neonates (< 35 weeks) in the first 24 h of life, where tracheal secretions were aspirated, transported, and cultured in a specific media. CLD was diagnosed as oxygen requirement at 28 days or 36 weeks post conceptional age.

Results: From 62 cultures, 7 were positive for U. urealyticum (11.3%, CI95%: 3.4-19.2%) and 3 were positive for M. hominis (4.8%, CI95%: 0-10.2%). From 53 neonates who were alive at 28 days after birth, 11 neonates needed oxygen (20.8%, CI95%: 9.8-31.7%). From 10 neonates with positive cultures, 2 (20%, CI95%: 0-44.8%) died, and from 8 alive neonates, 3 (37.5%, CI95%: 4.0-71.0%) survived without CLD. From 52 neonates with negative cultures, 7 (13.5%, CI95%: 4.2-22.7%) died, and from 45 alive neonates, 39 (86.7%, CI95%: 76.7-96.6%) survived without CLD, and there was a significant difference between neonatal groups with positive and negative tracheal culture progressing to CLD (62.5% vs. 13.3%) (P < 0.001) (Figure 1).

Conclusions: Intrauterine infection with U. urealyticum and M. hominis leads to negative neonatal outcome and increased rate of chronic lung disease in preterm neonates (< 35 weeks).

Keywords: Ureaplasma urealyticum; Mycoplasma hominis; Lung Diseases; Infant; Premature

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►Implication for health policy/practice/research/medical education:

Preterm neonates are at risk for severe infections and they might progress rapidly to death. Understanding the relative infection rate of some unusual infections, such as ureaplasma and mycoplasma and their role in neonatal pneumonia or late squeals, such as chronic lung disease would help us in better treatment modalities.

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1. Background

Ureaplasma spp. can be found on the mucosal surfaces of the cervix or vagina of 40 to 80% of sexually mature asymptomatic women, whereas *M. hominis* may occur in 21 to 53% (1). Intrauterine infection is a major cause of preterm labor and different organisms can be cultured in approximately half of all preterm births, especially those occurring at less than 30 weeks of gestation, so increasing neonatal risk of congenital infections. Vertical transmission of *ureaplasma* spp. has been reported to range from 25 to 60% and isolation rates vary inversely with gestational age and maternal socioeconomic status, according to most studies (1, 2). Respiratory disease remains the most common cause of perinatal morbidity and mortality, especially in preterm neonates and *ureaplasma* spp and *mycoplasma* are known as pathogens in congenital pneumonia. Very little information exists to indicate what are the long-term consequences that may result from neonatal infection by *ureaplasma* spp. or *M. hominis*. Three independent reports associating the presence of *ureaplasma* spp. in the lower respiratory tract with progression to chronic lung disease (CLD), and even death in very low birth weight neonates were published in 1988 (3-5). Pooled studies showed a significant association between *ureaplasma* colonization and development of CLD ($P < 0.001$) (3). But they did not show if medical treatment with erythromycin or other macrolodes might reduce the CLD incidence, and most of their sample sizes were not big enough to conclude if the routine culture for *ureaplasma* and treatment of colonization with the aim of preventing CLD should be done routinely or not (6, 7). So the association between the infection by those pathogens and CLD needs more clinical investigation.

2. Objectives

The colonization rate of preterm neonates with *U.urealyticum* and *M. hominis* and their long term sequel, such as CLD has been a matter of debate in recent years. A prospective study was performed to determine the relative incidence of tracheal cultures of preterm ventilated neonates with these organisms and development of CLD.

3. Patients and Methods

We have conducted a cohort prospective study in a neonatal intensive care unit (NICU) in Hazrat Rasoul Hospital in Tehran, Iran from September 2007 till March 2009. With all preterm neonates (< 35 weeks), where gestation needed mechanical ventilation, a sterile tracheal aspirate was taken in the first 24 hours after intubation and after infiltration in a transport media (phosphate-buffered saline), and it was cultured in highly specific media for *ureaplasma* and *mycoplasma*. Totally 80 samples were taken, from which 18 (22.5%) samples were not adequate (with different causes, 3 cases were dried samples, 4 were not transported with a transport media, 5 neonates had a gestational age more than 35 weeks, and 6 samples were taken from nasopharyngeal secretions instead of tracheal secretions.) and 62 samples were cultured. CLD or bronchopulmonary dysplasia was defined as oxygen requirement at 28 days after birth or 36 weeks post-conceptional age. Data analysis was done with Fisher exact test and T-test using SPSS 15.

4. Results

From 62 samples received by the laboratory, 10 samples (16.1%, CI95%: 7.0-25.3%) were positive, 7 (11.2%, CI95%: 3.4-19.2%) had *U.urealyticum*, and 3 (4.8%, CI95%: 0-10.2%) had

Table 1. The Relationship between Positive Tracheal Culture and Neonatal Characteristics

Tracheal Culture Results		Positive, n = 10	Negative, n = 52	Total, n = 62	P
Gender	female	4, 40	24, 46.1	28, 45.1	0.722
	male	6, 60	28, 53.8	34, 54.8	
PROM	positive	4, 40	15, 28.8	19, 30.6	0.418
	negative	6, 60	37, 71.1	43, 69.3	
Maternal Steroid	yes	7, 70	34, 65.3	41, 66.1	0.773
	no	3, 30	18, 34.6	21, 33.8	
Maternal Fever	yes	3, 30	7, 13.4	10, 16.1	0.190
	no	7, 70	45, 86.5	52, 83.8	
Route of Delivery	cesarean section	8, 80	32, 61.5	40, 64.5%	0.262
	vaginal delivery	2, 20	20, 38.4	22, 35.5%	
Final Outcome	alive to discharge	8, 80	45, 86.5	53, 85.5%	0.593
	death before discharge	2, 20	7, 13.4	9, 14.5%	
Needs Oxygen after 28 days	yes	5, 62.5	6, 13.3	11, 20.7	< 0.001
	no	3, 37.5	39, 86.6	42, 79.2	
Gestational age (wks), Mean \pm SD		28.1 \pm 1.8	31.5 \pm 2.9	30.2 \pm 3.3	< 0.001
Weight, g, Mean \pm SD		1050.7 \pm 354.4	1485.1 \pm 425.7	1290.1 \pm 560.6	0.003

Mycoplasma Hominis (Table 1). None were positive with both microorganisms.

From all 62 neonates, 18 (29%) weighted less than 1000 g, 29 (46.7%) weighted between 1000 to 1499 g, and 15 (24.1%) weighted between 1500 to 2500 g.

Mean \pm SD of birth weight of neonates with positive cultures were 1050.7 ± 354.4 g and neonates with negative culture had a mean birth weight of 1485.1 ± 425.7 g that showed statistically significant difference ($P = 0.003$) (Table 1). There was also statistically significant difference in mean gestational age between neonates with positive and negative culture (28.1 ± 1.8 weeks vs. 31.5 ± 2.9) ($P < 0.001$) (Table 1). There was no statistically significant difference in other parameters such as maternal steroid administration in last week before delivery, maternal fever, route of delivery, prolonged premature rupture of membranes (more than 24 hours), or maternal antibiotic usage among these two groups (Table 1). Nine neonates died in the first month of life (5%). The other 53 alive neonates (85.4%) were followed till discharge from hospital, and 11 (20.7%) of them needed supplemental oxygen after 28 days of life (Figure 1). From 10 neonates with positive cultures, 2 (20%) died, and from 8 alive neonates, 5 (62.5%) had CLD and 3 (37.5%) survived without CLD. From 52 neonates with negative cultures, 7 (13.4%) died, and from 45 alive neonates, 6 (13.3%) had CLD and 39 (86.6%) survived without CLD ($P < 0.001$).

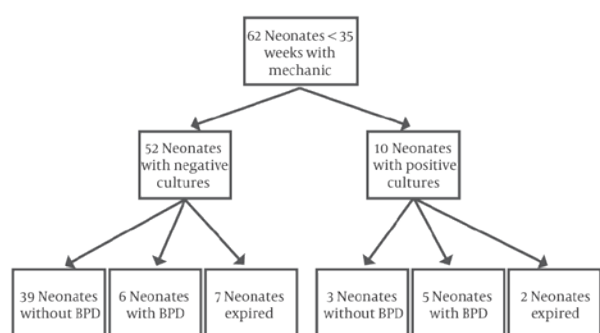


Figure 1. Summary of the Results and Outcome of 62 Neonates (< 35 Weeks) with Mechanical Ventilation

5. Discussion

The genital *mycoplasmas* and *ureaplasmas* represent a group of microorganisms that have been associated with different patterns of infection in pregnant mothers and their infants. With better laboratory detection and increasing knowledge about their significance in maternal and neonatal infections, this situation is now changing (8), as high as 40 to 80% of women have been reported to be colonized with genital *mycoplasmas* (9). Their role in infertility, post-partum endometritis, chorioamnionitis, preterm labor, and spontaneous abortion has been extensively investigated. In Iran, Badami reported *M.hominis*

was isolated from 35% and *U.urealyticum* was isolated from 33% of infertile females compared with 7.2% of normal population (10), and Najari Peerayeh reported a 37.4% detection rate with PCR for *mycoplasmas*, from which 22.5% were positive with *U.urealyticum* in infertile Iranian women (11).

The fetus can be infected via three different routes: vertical transmission from infected amniotic fluid, hematogenous spread from the placenta, and birth through infected vaginal canal. Vertical transmission rates among neonates born to colonized women are 25-60%. Colonization rate of the neonates is adversely related to their gestational age and birth weight and has been shown to be 60% in neonates under 1000 g, 15% in neonates 1000-1500 g, and 10% in term neonates (1). *Ureaplasma* has been implicated in neonatal morbidity and mortality including congenital pneumonia, preterm delivery, low birth weight, and intrauterine growth retardation, and it is thought to infect or colonize up to 37% of newborns. Heggie (12) et al. showed from tracheal aspirate specimens, *U. urealyticum* was recovered from 17% (37) and *M. hominis* from 2% (4). Although neonates with positive results were less mature than their cohorts with negative results, there were no substantive differences in clinical outcomes between the two groups. In India, 20% (20) of the study neonates were colonized with *U. urealyticum* and they showed the mean gestational age of the neonates in the colonized group was less than that of non-colonized neonates ($P < 0.05$) (13). We have shown a prevalence rate of 11% for *ureaplasma* and 5% for *mycoplasma* with more infection rate in less premature neonates as well. None of the 20 babies colonized with *U. urealyticum* in Pandey study developed CLD as compared with two (2.5%) of the non-colonized group, and they suggested colonization of the airways with *U. urealyticum* had no significant role in development of CLD in Indian preterm infants. The association between presence of *ureaplasma* and the development of CLD remains controversial and hotly debated. In 1995, a meta-analysis by Wang et al. included 1479 babies from 17 studies (14), reporting a significant association between CLD diagnosed at 28 days of life and *ureaplasma* colonization, with an overall relative risk of 1.72 (CI95%: 1.5-1.96). In a cohort of 126 preterm deliveries, Kafetzis et al. (15) found a significant increase in CLD as well as mortality among *ureaplasma* colonized infants. Van Waarde et al. (16) found that *Ureaplasma* was significantly associated with both CLD and lower gestational age, but logistic regression analysis failed to show a correlation between *ureaplasma* colonization and CLD. Schelonka et al. (17) found an odds ratio (OR) of 2.83 (CI95%: 2.29-3.51) for the relationship between the presence of *ureaplasma* and CLD in a meta-analysis of 23 studies, and Goldenberg et al. (18) confirmed a probable association between infection and CLD as well. Waites studied the colonization rate of *U. urealyticum* and a significant trend toward higher neonatal morbidities such as longer ventilation and hos-

pital stay and CLD (3). The etiology of bronchopulmonary dysplasia (BPD) is multifactorial and complex. Development of BPD is associated with prenatal and postnatal factors that lead to an arrest of lung development. Prenatally, maternal chorioamnionitis is associated with later development of BPD, with *U.urealyticum* being the most common association with chorioamnionitis at less than 30 weeks of gestational age (19). Postnatal insults include oxygen toxicity, barotrauma and volutrauma from mechanical ventilation, and sepsis. These additional insults lead to activation of the inflammatory cascade and significantly increase the risk of BPD. In recent years, an appreciation for the role of inflammation as a consequence of perinatal infection emerged as an important factor in the pathogenesis of BPD. Some proinflammatory cytokines [interleukin- β (IL- β), tumor necrosis factor alpha, and IL-6 and 8] are shown to have an important role in different neonatal pathologies such as cerebral palsy (20) and CLD (21). Dyke *et al.* found that the route of delivery might have a role in risk of developing BPD, and those who have been delivered by cesarean section and had positive gastric aspirate with *ureaplasma* had a higher rate of progressing to BPD (21). We have shown a greater incidence of BPD in culture positive neonates (50%) in comparison to culture negative infants (11.5%), but they did not show any significant difference in their route of delivery or weight or other demographic factors. As there are conflicting results regarding infection-BPD association, some studies have reported the results of antibiotic therapy in colonized infants. Two small randomized clinical trials of erythromycin therapy in high risk neonates with tracheobronchial colonization of *ureaplasma* failed to show any difference between treated and non-treated neonates in the development of BPD (22, 23). It is evident from different studies that in a group of preterm infants, colonization with genital *mycoplasmas* have negative effects in their outcome, where it is not known which infant progresses to CLD at this time and some neonates might not show benefit from antibiotic therapy for their infection, and this matter needs further investigation.

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Authors' Contribution

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