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Ureaplasma infections in pre-term infants: Recent information regarding the role of *Ureaplasma* species as neonatal pathogens

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Although numerous clinical observational studies have been conducted over a period of over 30 years, the clinical significance of *Ureaplasma* infection is still under debate. The *Ureaplasma* speices. is a commensal in the female genital tract and considered to have of low virulence; however, *Ureaplasma* colonization has been associated with infertility, stillbirth, preterm delivery, histologic chorioamnionitis, and neonatal morbidities, including congenital pneumonia, meningitis, bronchopulmonary dysplasia, and perinatal death. Recently, *Ureaplasma* was subdivided into 2 separate species and 14 serovars. *Ureaplasma parvum* is known as biovar 1 and contains serovars 1, 3, 6, and 14, and *Ureaplasma urealyticum* (biovar 2) contains the remaining serovars (2, 4, 5, and 7-13). The existence of differences in pathogenicities of these 14 serovars and 2 biovars is controversial. Although macrolides are the only antimicrobial agents currently available for use in neonatal ureaplasmal infections, in the current clinical field, it is difficult to make decisions regarding which antibiotics should be used. Future investigations involving large, multicenter, randomized, controlled studies are needed before proper recommendations can be made for clinical practice.

Key words: *Ureaplasma parvum*, *Ureaplasma urealyticum*, Neonatal pathogen, Prematurity

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Introduction

Ureaplasma species are the most common bacteria detected in urogenital infections, including nongonococcal urethritis in men and multiple obstetrical complications in women[1, 2]. Since *Ureaplasma* spp. can be found in vaginal flora in 40% of sexually inactive and 67% sexually active women, it is known as a commensal in the female genital tract[3].

Although numerous clinical observational studies were conducted over a period of over 30 years, the clinical significance of these bacteria is still under debate[4]. These bacteria are considered to be of low virulence; however, *Ureaplasma* colonization has been associated with infertility[5], stillbirth[6], preterm delivery[7, 8], histologic chorioamnionitis[9], and perinatal death in neonates[10].

This article summarizes recent information on the role of *Ureaplasma* infection in diseases in preterm infants and future considerations.

Ureaplasma spp.

1. Classification and characteristics

Ureaplasma spp. is a member of the Mollicutes class, which is comprised of 4 orders, 5 families, 8 genes, and nearly 200 known species, 17 of which are known to use humans as their primary host[4]. Another well-known member of the *Mollicutes* class is *Mycoplasma* spp., in which there are 3 species, *Mycoplasma hominis, Mycoplasma genitalium, and Mycoplasma fermentans*, which are known to occur in the female urogenital tract. *Ureaplasma* was first described by Shepard in the 1950s and were detected in the male urethritis[11]. Recently, *Ureaplasma* was subdivided into 2 separate species and 14 serovars that have been grouped according to 16S dRNA sequencing results into 2 genetically related biovars[3, 4].

U. parvum, known as biovar 1, contains serovars 1, 3, 6, and 14, and *U. urealyticum* (biovar 2) contains the remaining serovars (2, 4, 5, and 7-13)[12]. Characteristics of all serovars include lack of cell walls, limited biosynthetic abilities, small genome size, and mucosal association in the human host[3]. The unique characteristic of *Ureaplasma* is their ability to hydrolyze urea to generate metabolic energy[1, 4]. Some debates still occur regarding whether there is a difference in pathogenicity exists among these 14 serovars and 2 biovars.

2. Virulence factors

Ureaplasma can directly activate the first component of complements and attach to host erythrocytes, neutrophils, spermatozoa, and urethral epithelial cells[1]. This can induce inflammation in humans and produces multiple manifestations of clinical diseases[4]. Since *Ureaplasma* spp. metabolizes urea to generate energy, it also produces secretory products such as ammonia, which may induce a local cytotoxic effect.

Previously reported ureaplasmal virulence factors include IgA protease, urease, phospholipases A and C, and production of hydrogen peroxide[13]. These factors may allow the organism to evade mucosal immune defenses by degrading IgA and injuring mucosal cells through the local generation of ammonia, membrane phospholipid degradation, prostaglandin synthesis, and membrane peroxidation[3]. Although phenotypic production of IgA protease and phopholipases was described several years ago, genome examination of multiple serovars has failed to reveal genes encoding these enzymes[4].

The multiple-banded antigen (MBA) of *Ureaplasma* spp. is the predominant antigen recognized during the infection process and may be involved in host inflammatory response stimulation. It undergoes a high rate of variation in vitro and exhibits variable sizes in vitro on invasive isolates, suggesting that antigen size variation may be another mechanism through which the organism evades host defenses[3, 4]. *Ureaplasma* serovars have multiple MBA genes, and some contain multiple copies of the same type of MBA gene.

3. Vertical transmission and intrauterine infection

Ureaplasmas can be isolated from endotracheal aspirations in up to 40% of newborn infants within 30 minutes to 24 hours after delivery[14, 15], and from maternal and umbilical cord blood at these delivery times[16]. This provided evidence that vertical *Ureaplasma* transmission and neonatal infection may occur in newborn infants. Additionally, recovery of *Ureaplasma* from the chorion increased with the duration of membrane rupture, suggesting an ascending route of infection[17]. Those born weighing less than 1,000 g are at higher risk of infection when the mother is colonized at up to 90% of the infection rate[18]. The possible pathogenesis involves fetal exposure to ascending ureaplasmal intrauterine infection, passage through an infected birth canal, hematogenous dissemination through the placenta into umbilical vessels, and colonization of the skin, mucosal membranes, respiratory tract, and dissemination into the blood and central nervous system[19, 20].

Intrauterine infection is now believed to be a major cause of preterm birth, particularly in gestations of less than 30 weeks[21]. *Ureaplasma* spp. is the most common isolate identified in amniotic fluid. Isolated *Ureaplasma* spp. from the chorioamnion has been consistently associated with histologic chorioamnionitis, which is inversely related to birth weight[22]. Several experimental studies with intra-amniotic inoculation of *U. parvum* showed that it did not stimulate premature labor in mice[23] or sheep[24], but did stimulate progressive uterine contractions and preterm delivery in rhesus macaques[25]. The Rhesus macaque experimental result suggests that species differences result in differences in host response or serovar differences in virulence.

Ureaplasma spp. infection in neonatal pathogens

1. Congenital pneumonia in preterm infants

In the mid-1970s, some investigators suggested a potential role for *Ureaplasma* in neonatal respiratory disease after isolation of these organisms from lungs of stillborn infants with peumonitis[26]. Evidence that *Ureaplasma* spp. cause congenital pneumonia includes isolation of bacteria in pure culture from amniotic fluid, affected lungs of neonates less than 14 hours after birth in the midst of an acute inflammatory response, and chorioamnion[1, 20]. Other evidence includes demonstration of a specific IgM response in the neonate[27], radiographic changes indicative of pneumonia

in culture-positive infants[28], demonstration of the bacteria in lung tissue using immunofluorescence[29], and electron microscopy[27].

2. Bacteremia and systemic infections

Ureaplasma isolation from cord blood was first described in 1969[30] and in a recent prospective study it was shown that 23% of infants had a positive cord blood culture for this organism[31]. Cassell et al.[32] reported that 26% of neonates culture-positive for *Ureaplasma* spp. in the lower respiratory tract were bacteremia with these organisms. *Ureaplasma* has been isolated from gastric aspirates, blood, cerebrospinal fluid (CSF), lung, and brain tissue, although this organism is most commonly isolated from respiratory secretions[3]. In 2 recent large prospective cohorts, *Ureaplasma* was detected in 17% of cord blood cultures and 23.6% of serum or CSF polymerase chain reaction (PCR) samples, with *U. parvum* as the predominant species detected in serum and CSF[10, 31].

3. Meningitis and neonatal brain injury

The largest recent prospective survey of invasive infections analyzed samples from 313 very low-birth-weight (VLBW) infants with suspected sepsis/meningitis or hydrocephalus reported that the risk of severe intraventricular hemorrhage (IVH) (≥grade 3) was 2.5-fold higher in serum PCR-positive than PCR-negative infants after adjustment for gestational age, but there was no association of cranial ultrasound abnormalities with detection of *Ureaplasma* in CSF[10].

A role for *Ureaplasma* in neonatal brain injury is supported by recent studies in experimental animal models[23]. In the murine intrauterine *U. parvum* infection model, the brains of fetal and newborn mice showed evidence of microglial activation, deleted myelination, and disturbed neuronal development. Future studies are needed to provide additional information regarding mechanisms of *Ureaplasma*-mediated brain injury.

4. Role of *Ureaplasma* infection in lung injury and inflammation

Some investigators found that *Ureaplasma* isolated from lower respiratory tract colonization is associated with peripheral blood leukocytosis, particularly the neutrophil component[29, 33]. Crouse et al.[28] evaluated chest radiographs of 44 preterm infants with *Ureaplasma* colonization the lower respiratory tract in comparison with those who were culture-negative. They found that pneumonia was twice as common in the *Ureaplasma*-positive group and early radiographic emphysematous changes within 2 weeks of birth were significantly more common in the *Ureaplasma*-positive group. In a recent cohort study of infants less than 33 weeks gestation, *Ureaplasma* spp. were detected during the first week of life in tracheal aspirates or nasopharyngeal aspirates in 35% of infants[10]. These findings suggest an in utero onset of inflammatory responses and lung injury[3].

Ureaplasma infection in neonate promotes a proinflammatory cytokine cascade in the lower respiratory tract; this infection is associated with an increase in tumor necrosis factors (TNF)-α, interleukin (IL)-1β, and IL-8[20] and blocks expression of the regulatory cytokines IL-6 and/or IL-10[4]. Viscardi et al.[33] examined pathological specimens from *Ureaplasma*-infected infants and reported that Transforming growth factor (TGF)-β1 expression increased in infants with pneumonia compared with control specimens. Li and coworkers[34] demonstrated that human macrophages exposed to the *Ureaplasma* antigen produce TNF-α and IL-6, and *Ureaplasma*-exposed macrophages release vascular endothelial growth factor and intracellular adhesion molecule-1.

Animal models, such as mouse and primate models, have contributed substantially to the understanding of how the inflammatory potential of ureaplasmal infection induces a deregulated, proinflammatory, interstitial pneumonitis leading to a profibrotic state[35, 36].

5. Association of *Ureaplasma* infection with development of bronchopulmonary dysplasia

The classic definition of bronchopulmonary dysplasia (BPD), a supplemental oxygen requirement at 28 days of age, has been criticized since widespread antenatal corticosteroid treatment, postnatal exogenous surfactant therapy, and gentler ventilator strategies in VLBW infants, a "new" BPD, emerged. Recently, Bancalari et al.[37] defined BPD as an oxygen requirement and the presence of radiographic abnormalities at 36 weeks postmenstrual age.

Since BPD etiology is multifactorial and complex, the relationship of *Ureaplasma* respiratory tract colonization with the development of BPD has been debated. In 1988, 3 independent groups published results of cohort studies linking BPD development with airway colonization with *Ureaplasma*[18, 32, 38]. A meta-analysis of 17 clinical studies published before 1995 supported a significant association between *Ureaplasma* respiratory tract colonization and BPD development. Another recent meta-analysis conducted by Schelonka et al.[39], who analyzed 36 cohort studies published between 1988 and 2004 involving approximately 3000 preterm infants, showed a significant association between *Ureaplasma* respiratory colonization and BPD development whether it was defined as oxygen dependence at 28 days (P<0.001) or at 36 weeks postmenstrual age (P<0.001). Other studies support the *Ureaplasma* respiratory colonization-BPD association, particularly in the subset of *Ureaplasma*-colonized infants exposed to chorioamnionitis and leukocytosis at birth[3].

Castro-Alcaraz et al.[40] observed that persistent, but not transient, *Ureaplasma* respiratory complications are significantly higher in colonized infants. Mortality due to respiratory complications is significantly higher in colonized infants and the risk of a combined outcome measure of BPD or death due to lung disease was 4.2-fold higher in colonized *Ureaplasma* rather than in noncolonized VLBW infants[14, 32].

Infants with BPD have elevated proinflammatory cytokines such as IL-1, IL-6, and IL-8, with IL-8 acting as a potent neutrophil chemoattractant and, as a result, theses infants have elevated neutrophils in the lungs[20]. Perinatal *Ureaplasma* infection may promote the inflammatory cascade in the lung and impair alveolar development directly or in conjunction with oxidant and ventilator-induced lung injury[3, 20]. Hence, postnatal application of high oxygen concentrations and mechanical ventilation and duration of exposure may potentiate the effect of *Ureaplasma*-associated injury to the lungs.

Treatment of *Ureaplasma* infection in preterm infants

Although it is known that macrolides are the only antimicrobial agents currently available for use in the treatment of neonatal ureaplasmal infections, in the clinical field it is difficult to make decisions regarding which antibiotics should be used. Due to its toxicity, doxycycline is not an alternative unless *U. urealyticum* is isolated from CSF. Clindamycin has also been used to successfully treat systemic *M. hominis* infections in infants[1]. As such, making specific recommendations for treating neonatal ureaplasma infections is difficult because the spectrum of ureaplasmal disease has not been fully described and there are very few clinical studies indicating the *in vivo* efficacy of antibiotics[1]. Therefore, not only are choices between limited drug options controversial, but also the actual indications concerning conditions under which treatment should be offered, dosage, and duration of therapy is debated.

Antibiotic therapy is a standard treatment modality for premature rupture of membranes (PROM). However, standard regimens failed to eradicate organisms including *Ureaplasma* or diminish inflammation in the amniotic cavity with PROM[41]. In an experimental *Ureaplasma* intraamniotic infection (IAI) in Rhesus monkeys, azitromycin alone or in combination with dexamethasone and indomethacin prevented fetal lung damage[42].

Despite the in vitro susceptibility of *Ureaplasma* to erythromycin, trials of erythromycin therapy in the first few weeks of life in *Ureaplasma*-colonized preterm infants have failed to demonstrate efficacy in preventing BPD[3]. Recently, Walls and colleagues[43] demonstrated that azithromycin prophylaxis, but not erythromycin, improved outcomes and reduced inflammation in a murine neonatal *Ureaplasma* infection model. This finding suggests that azithromycin is effective if administered immediately after birth. However, there have been no published investigations of azithromycin in neonates regarding low birth weight infants. Hence, until appropriate pharmacokinetics and efficacy trials are conducted, a dosing regimen for azithromycin in neonates cannot be recommended[41].

Conclusions and future perspectives

Recent clinical and experimental studies have shown significant evidence that *Ureaplasma* infection may induce inflammatory processes early in utero and, as a result it can cause intrauterine chorioamnionitis, postnatal systemic infection, and lung injury, including BPD. However, more studies are needed to determine the relationship of *Ureaplasma* virulence factors, host immune factors affecting pathogen susceptibility, and inflammatory variability, and interactions with environmental factors such as oxygen exposure and mechanical ventilation[3]. Furthermore, a study analyzing antimicrobial therapy of *Ureaplasma*-colonized infants should be conducted in a large, multicenter, randomized clinical trial to determine whether these antibiotics are effective in reducing BPD rate and improving neonatal outcomes.

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