Role of *Ureaplasma* Respiratory Tract Colonization in Bronchopulmonary Dysplasia Pathogenesis

Current Concepts and Update

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KEYWORDS

- *Ureaplasma parvum* • *Ureaplasma urealyticum* • Prematurity
- Bronchopulmonary dysplasia • Macrolide antibiotics

KEY POINTS

- Meta-analyses of clinical studies over the past 30 years have confirmed ureaplasma respiratory colonization as an independent risk factor for bronchopulmonary dysplasia (BPD) but have not established causality.
- Experimental infection models in sheep and nonhuman primates have demonstrated that *Ureaplasma* can establish a chronic infection with inflammation in the intrauterine compartment and alter fetal lung development.
- Although *U parvum* serovars are the most commonly isolated serovars from clinical samples, no specific serovar or virulence factor has been identified in association with BPD.
- There is currently insufficient data concerning the benefit/risk ratio of antibiotic therapy to recommend treatment guidelines to prevent BPD in preterm infants at risk for or with confirmed ureaplasma infection.

INTRODUCTION

The mycoplasma species *Ureaplasma parvum* and *U urealyticum* are genitourinary tract commensals in adults but are associated with adverse pregnancy outcomes[1] and neonatal morbidities of prematurity, including bronchopulmonary dysplasia

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(BPD),[2] necrotizing enterocolitis,[3] and severe intraventricular hemorrhage.[4] These organisms are the most commonly isolated organisms from infected placentas and amniotic fluid.[1,5] They have been detected in cord blood,[4,6] cerebrospinal fluid,[4] respiratory secretions,[2,7] gastric aspirates,[8] and brain[9] and lung tissue[10] of preterm infants. This review focuses on the epidemiologic and experimental evidence for a causal role of *Ureaplasma* species in BPD pathogenesis and implications for therapeutic interventions.

UREAPLASMA SPECIES

The 14 *Ureaplasma* serovars are grouped in 2 species, *U parvum* (serovars 1, 3, 6, and 14) and *U urealyticum* (serovars 2, 4, 5, and 7–13) (**Box 1**). These organisms are among the smallest free-living, self-replicating cells. They lack cell walls, hydrolyze urea to generate ATP, have limited biosynthetic functions, and adhere to human mucosal surfaces of the genitourinary tract in adults and respiratory tract in newborns.[11] The authors' group and others have recently demonstrated that most *Ureaplasma* isolates from neonatal and adult clinical specimens as well as American Type Culture Collection (ATCC) reference strains have the capacity to form biofilms in vitro.[12,13] If biofilm formation is confirmed in vivo, it may be another mechanism by which *Ureaplasmas* evade the host immune response and increase resistance to antibiotics.

U parvum serovars are the most common serovars detected in neonatal respiratory samples at all gestational ages. In a prospective preterm cohort in a single institution, *U parvum* was detected in 63% of respiratory isolates.[7] Serovars 3 and 6 alone and in combination accounted for 96% of *U parvum* respiratory isolates in this cohort.[7] *U urealyticum* isolates were commonly a mixture of multiple serovars, with serovar 11 alone or combined with other serovars (59%) as the most common serovar. Most studies have not observed differences in prevalence of either species or specific serovars

Box 1
Characteristics of genital mycoplasmas isolated from preterm infants

- Two species
  - *U parvum* (serovar 1, 3, 6, and 14)
  - *U urealyticum* (serovars 2, 4, 5, 7–13)
- Small genomes (limited biosynthetic abilities)
- Lack cell walls (susceptible to desiccation and heat)
- Hydrolyze urea to generate ATP
- Biofilm-forming capacity demonstrated in vitro and in vivo[12,13,95]
- *U parvum* serovars most common in clinical specimens (70%)[7]
- Require special transport and culture media to support growth
- Virulence factors
  - Urease production of ammonia
  - IgA protease (degrading mucosal IgA)
  - Hydrogen peroxide (membrane peroxidation)
  - Phospholipases A and C (membrane phospholipid degradation)
  - Inhibition of host cell antimicrobial peptide expression[22]
  - Serine//threonine kinase and protein phosphatase (cytotoxicity)[20]
  - Multiple-banded antigen, major pathogen-associated molecular pattern of *Ureaplasma* serovars recognized by host immune system: size variations evade immune detection[24,53,96]

Abbreviation: IgA, immunoglobulin A.