



Study of *Ureaplasma urealyticum* and *Ureaplasma parvum* in Congenital Pneumonia

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ABSTRACT

Congenital pneumonia is one of the common causes of respiratory distress at birth with significant morbidity and mortality in infants. *Ureaplasma urealyticum* and *Ureaplasma parvum* are the commonest atypical bacterial causes. Clinically, congenital pneumonia is often difficult to diagnose owing to poor specificity of clinical signs, similarities in radiologic presentation with other respiratory conditions of the newborn. Isolation of these bacteria by culture from nasopharyngeal aspirates or tracheal aspirates obtained within 8 h of life is the gold standard of diagnosis. However, this technique is elaborate and time consuming in identifying atypical bacteria. Polymerase chain reaction may replace culture as a more sensitive diagnostic aid.

Keywords: Newborn, Atypical Bacterial, Congenital, Pneumonia

INTRODUCTION

Pneumonia is an infection of the lungs, characterized mainly by inflammation of the microscopic air sacs called alveoli. In neonates, pneumonia is classified as congenital or neonatal in origin depending on the time or period of acquisition of infection. Based on the Oxford Medical Dictionary, the word 'congenital' is defined as a condition that is recognized at birth or believed to have been present since birth. It is therefore defined as 'pneumonia with clinical and radiological evidence present at birth' (Cassell *et al.*, 1983), with a positive identification of the causative organism from either nasopharyngeal aspirates, (Cassell *et al.*, 1983; Muhe *et al.*, 1999; Lehmann *et al.*, 1999) tracheal aspirates obtained aseptically within 8 h of life, (Sherma *et al.*, 1980) or gastric aspirates obtained within 1-2h after birth (Huang *et al.*, 1998). Congenital pneumonia is one of the common causes of respiratory distress at birth with significant morbidity and mortality in infants. The actual incidence of this condition is not known. Large population studies on the incidence of this condition based on clearly defined diagnostic criteria is lacking. Neonatal pneumonia including congenital pneumonia has been reported to contribute an estimated 750 000 to 1.2 million neonatal deaths annually (The Child Health Research Project, 1999). Bacteria, virus and fungi are known causative organisms. Atypical bacterial pathogens reportedly known as causative agents include *Ureaplasma*

urealyticum, *Ureaplasma parvum*, *Mycoplasma hominis*, *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, *Listeria monocytogenes*, *Mycobacterium tuberculosis* and *Treponema pallidum*. Prompt diagnosis of this condition is often difficult owing to the poor specificity of clinical manifestations and respiratory signs. Chest radiographic appearances are not specific for pneumonia as it may mimic other features in conditions such as respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN) or aspiration syndrome. Routine microbiological culture remains the gold standard in laboratory diagnosis. However, more sensitive tests such as polymerase chain reaction (PCR) may improve diagnosis with a shorter duration. This review focuses on the ureaplasmas in this neonatal condition, issues in the laboratory diagnosis and management strategies including preventive measures.

Ureaplasma urealyticum

Ureaplasma urealyticum is a eubacteria that have evolved from clostridia-like gram-positive cells by gene deletion (Taylor-Robinson & Furr, 1998). It belongs to the class Mollicutes known as the smallest free-living organisms. Its genome is comprised of 947kbp (711 genes). All

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serovars lack cell walls but are bound by cell membrane, resistant to β -lactam antibiotics, possess small genome size, mucosal association in the human host and limited biosynthetic abilities (Viscardi, 2010). Recently, *Ureaplasma* was split into 2 separate species and 14 serovars. *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 (Robertson *et al.*, 2002).

U. urealyticum exists as normal commensal flora in the reproductive tract of adults especially women. It can be isolated from the vagina of 40% to 80% of sexually active asymptomatic women (Cassell *et al.*, 2001). Colonization occurs as a result of sexual activity especially with multiple partners, younger age, low socio-economic status, black ethnicity and oral contraceptive use (Matlow *et al.*, 1998). Routes of transmission from an infected mother to the fetus are before birth (in utero) or at birth via passage through a colonized birth canal (Cassell *et al.*, 2001; Cassell *et al.*, 1983). Major virulence factor for adherence to human cells is adhesins. Cleavage of protease IgA may enable ureaplasmas to colonize and invade the cervix and upper genital tract of pregnant women (Glass *et al.*, 2000).

Early work on the possible role of *Ureaplasma* spp as a pathogen in neonatal respiratory infections arose in the mid-1970s, when Tafari and colleagues described the isolation of these organisms from lungs of stillborn infants with pneumonitis (Tafari *et al.*, 1976). Recovery of *U. urealyticum* from the lower respiratory tract of newborn infants has been linked to pneumonia and persistent pulmonary hypertension (Waites *et al.*, 1989). Crouse *et al.* (1993) further isolated *U. urealyticum* from endotracheal aspirates of newborn infants in the absence of other respiratory pathogens and was significantly associated with radiographic pneumonia (Crouse *et al.*, 1993). In a study of 100 low birth weight infants, congenital pneumonia was evident in three of seven infants with positive *U. urealyticum* tracheal aspirate culture (Seith *et al.*, 1999). In another series of autopsies involving 159 neonates, *U. urealyticum* was one of the isolates (9%) and congenital pneumonia was a major outcome (Madan *et al.*, 1988). Panero *et al.* (1995) reported isolation of *U. urealyticum* from 16 (55.2%) of tracheal aspirates and/or blood specimens of 29 neonates with acute respiratory

disease. Pneumonia was diagnosed more frequently in *U. urealyticum* positive infants compared to those who were negative. Their findings suggested that *U. urealyticum* can induce an inflammatory response in selected individuals who present with clinical, radiological or histological features of pneumonia (Panero *et al.*, 1995).

Culture is the gold standard for diagnosis of *U. urealyticum* infections. However it is elaborate, takes too long to yield, usually within 2-5 days, expensive and not available in most centers. Furthermore, reports on culture studies have shown detection rates to be as low as 80% in typical clinical laboratory conditions, but, research laboratories report higher sensitivities (Blanchard *et al.*, 1993).

Although Quinn *et al.* (1986) suggested that type-specific antibody response greater than or equal to 1:32 against certain ureaplasma serovars occur in infants with respiratory disease and in women with pregnancy wastage compared with control patients, there is need for more studies to fully appreciate the value for antibody determination in this population (Quinn, 1986). Microimmunofluorescence test (MIF), metabolic inhibition and enzyme immunoassay (EIA) are serological tests that have been used for *Ureaplasma* species but, only in research setting. No assays for genital mycoplasmas have been standardized and made commercially available in the United States (Waites *et al.*, 2005).

Recently, great attention has been given to the application of PCR assay in the primary detection of ureaplasma perinatal infections because PCR assay is fast, does not necessarily require viable organisms and limits of detection is better than culture. Blanchard *et al.* (1993) compared results of culture and PCR analysis of 95 endotracheal aspirates of newborn infants and found 99% agreement between culture and PCR (Blanchard *et al.*, 1993). Other reports have shown greater sensitivity of PCR in comparison to culture (Yoon *et al.*, 2003; Castro-Alcaraz *et al.*, 2002; Yoon *et al.*, 2000; Cinliffe *et al.*, 1996; Abele-Horn *et al.*, 1996) Real-time PCR has been reported to have higher sensitivity and specificity than culture and conventional PCR. Xiao *et al.* (2010) compared real-time PCR with conventional PCR and culture in the detection of human ureaplasmas (*U. parvum* and *U. urealyticum*). They reported that real-time PCR

had a sensitivity of 96.9% and specificity of 79.0% when compared with culture and a diagnostic sensitivity of 98.3% for *U. parvum* and 96.6% for *U. urealyticum* while specificity was 88.9% for *U. parvum* and 99.1% for *U. urealyticum*. (Xiao *et al.*, 2010). Compared to culture and traditional PCR, Xiao *et al.* (2010) and Cao *et al.* (2007) concluded that real-time PCR is the most sensitive assay for the detection of *Ureaplasma* species (Xiao *et al.*, 2010; Cao *et al.*, 2007)

Ureaplasma parvum

Ureaplasma parvum is part of the normal genital bacterial flora of both men and women. It is more common than *U. urealyticum* as a colonizer of the male and female urogenital tract (Robertson *et al.*, 2002). Their occurrence in pregnant women provides a reservoir for transmission to the fetus and neonate. *U. parvum* is associated with the development of chorioamnionitis, funisitis and preterm delivery. While it causes neonatal sepsis, bronchopulmonary dysplasia in premature babies, meningitis or even death (Waites & Taylor-Robinson, 2011]. There is little knowledge about the pathogenicity of *U. parvum* in term newborn infants. Morioka and colleagues reported the first and only case of *U. Parvum* being implicated in the pathogenesis of congenital pneumonia with sepsis in a human term newborn (Morioka *et al.*, 2010).

Ureaplasma parvum can be identified by culture, serology and PCR. Culture technique for detecting *U. parvum* requires special media and expertise that is not widely available (Waites *et al.*, 2005). Serological tests are mainly used as research tools and not recommended for routine diagnostic purposes. PCR is most suitable diagnostic tool. Morioka and colleagues detected *Ureaplasma parvum* from blood by multiplex PCR and from the placenta and umbilical cord by conventional PCR.

LABORATORY DIAGNOSIS

Culture technique

Nasopharyngeal aspirates or tracheal aspirates obtained aseptically before 8h of life are appropriate specimens that are cultivable on microbiological media. Sherman and coworkers

used tracheal aspirate obtained aseptically within 8 hours of life in diagnosing congenital pneumonia. The culture result yielded growth of bacteria from the tracheal aspirates of infected infants (Sherman *et al.*, 1980). However, conventional bacteriological culture is not useful in the recovery of atypical bacterial pathogens of congenital pneumonia. The cultures of genital mycoplasmas require different microbiological processing and media for cultivation. Culture for *C. trachomatis* involves isolation of the organism in tissue culture and confirmation of microscopic identification of the characteristic inclusions, by staining with a fluorescein-conjugated, species-specific monoclonal antibody (CDC, 2004).

Blood culture is useful in identifying the causative organisms, but not all cases of congenital pneumonia are associated with a positive blood culture. In a study by Sherman *et al.* (1980), blood culture was positive in 56% of 25 neonates with congenital pneumonia (Sherman *et al.*, 1980). However, it is not useful in isolating or identifying atypical bacteria. A major limitation in the use of culture for the diagnosis of atypical bacteria is that, it is elaborate, quite expensive, time consuming and not available in most centers. Techniques that may help overcome these limitations include serological tests, antigen detection, nucleic acid probes and PCR assays.

Serological tests

The use of serological tests to establish diagnosis have limited use, however, it may offer some insight. Serological tests for genital mycoplasma infections in infants remain problematic and used only in research settings. Although a number of serological test have proven useful in the diagnosis of *C. trachomatis* infections in neonates and infants, there are issues of sensitivity and specificity that limit their uses. Though lacking well-defined sensitivity, direct fluorescent antibody tests DFA are FDA-approved test for use in pharyngeal specimens. However, it has high specificity if a *C. trachomatis* specific stain is used. Enzyme immunoassays EIAs are not recommended for use in pharyngeal specimens due to lack of specificity. Microimmunofluorescence test which uses elementary bodies as antigen is the test of choice.

Nucleic Acid Amplification Tests

Nucleic acid amplification techniques (NAATs) have the potential to produce rapid, sensitive, and specific results, allowing early appropriate antibiotic therapy. Among the nucleic acid amplification tests, PCR was the first and still the commonest and most frequently applied nucleic acid-based test. PCR testing has increased the sensitivity of detection of many organisms, such as *C.trachomatis* and mycoplasmas. Comparisons of PCR detection of human ureaplasma to culture method in endotracheal aspirate samples from neonates show sensitivities of 91-95% (Cinliffe et al., 1996).

In multiplex PCR, several independent amplifications are carried out simultaneously in one tube with a mixture of primers. Studies have indicated that increase in the number of targets in one reaction results in reduced or loss of sensitivity (Tong et al., 1999).

While conventional PCR measures the end PCR product using gels or other method, real-time PCR uses fluorogenic probes which allow amplification and detection to occur simultaneously. Traditional PCR assays are gradually being replaced by real-time formats in which the same targets may be used. Sensitivity and specificity of real-time PCR has been reported to be identical to that of conventional PCR for *M. pneumoniae* [76,77], however Xiao et al (2010) and Cao et al., (2007) reported the test as superior for the detection of *U. urealyticum* and *U. parvum*. Although PCR is sensitive, this assay is not easily affordable and available as diagnostic tool especially in developing countries. Moreover, it is not a standardized test. This can prevent confirmation of diagnosis of congenital pneumonia caused by atypical bacteria.

TREATMENT

Antibiotic and Supportive Care

A positive isolation of organisms by culture or PCR assay from a normally sterile site in newborn infants with evidence of infectious inflammation is justified for treatment (Cassell et al., 2001). Antibiotics are a vital part of managing newborns with pneumonia. Macrolides, fluoroquinolones and tetracyclines are drugs of choice for ureaplasma infections.

Though, fluoroquinolones and tetracyclines are not allowed in neonatal and pediatric settings due to potential toxicity (Matlow et al., 1998). Erythromycin and new-generation macrolide such as azithromycin are effective in treating ureaplasma respiratory infections in neonates, but, treatment failures are known to occur (Waites et al., 2005; Waites et al., 1994). Moreover, clinical expertise in the use of azithromycin in treating ureaplasma neonatal infections is minimal and guidelines for their dosage and use is lacking. Oral erythromycin or ethylsuccinate 50mg/kg/d in four divided doses for 14 days is recommended for treating chlamydia pneumonia. A failure rate of about 20% have been reported in infants with Chlamydia pneumonia been treated with oral erythromycin, thus, requiring a second course of therapy (Hammerschlag et al., 1998). To date, fluoroquinolones or clarithromycin are alternatives to erythromycin. Problem with compliance and tolerance with erythromycin in newborns are frequent. In the event of intolerance, oral sulfisoxazole at a dose of 150mg/kg/d in four divided doses can suffice after the immediate newborn period (Darville, 2005). Duration of antimicrobial treatment depends on the clinical, radiological and microbiological response of the infants, varying between 5 days to 3 weeks.

Equally important in the management of congenital pneumonia are supportive measures. Respiratory insufficiency is often linked to infants with congenital pneumonia, hence, the need for ventilatory support. The use of ventilator support requires precautions to ensure that the airway pressure required to attain alveolar stability interfere as little as possible with alveolar perfusion, myocardial function and venous return. Other supportive measures include appropriate use of inotropes, meticulous fluid therapy to ensure electrolyte balance and nutrition by proper breast feeding. Surfactant therapy could be useful in preterm infants since lung effluents has been reported to have disturbed surface properties despite the presence of surfactant in sufficient amount (Rudiger et al., 2001).

Prevention

A major preventive measure for congenital pneumonia is active management of premature rupture of maternal chorioamniotic membranes. In a review of 14 randomized controlled trials,

administration of antibiotics after premature rupture of membranes was associated with a delay in delivery, reduction in maternal infection, chorioamnionitis and neonatal infections (Kenyon et al., 2004). Prenatal screening and treatment of pregnant women, especially those ages <25 years which are at high risk is the most effective strategy for preventing neonatal chlamydial infections.

Conclusion

Congenital pneumonia is a common cause of significant morbidity and mortality in neonates, especially among preterm infants. Congenital pneumonia should be suspected in any newborn infant with clinical features such as respiratory distress present at birth or shortly after birth and /or a chest radiographic presentation indicative of pneumonia and atypical bacteria should be suspected in infants with persistent pneumonia not responding to the WHO recommended first line antibiotics. Polymerase chain reaction has better sensitivity and specificity in the laboratory diagnosis of atypical bacteria. Consequently, appropriate antibiotic administration including supportive care should be started while proper techniques to identify these organisms are on.

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