CLINICAL MICROBIOLOGY REVIEWS, Oct. 2005, p. 757–789 Vol. 18, No. 4
0893-8512/05/$08.00+0 doi:10.1128/CMR.18.4.757–789.2005

Mycoplasmas and Ureaplasmas as Neonatal Pathogens

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INTRODUCTION

The first report of a mycoplasma to be recovered directly from a human and associated with a pathological condition occurred in 1937, when Dienes and Edsall isolated an organism which was probably the one known now as *Mycoplasma hominis* from a Bartholin's gland abscess (76). At that time, mycoplasmas were called pleuropneumonia-like organisms because the microbe now known as *Mycoplasma mycoides* had been shown to cause bovine pleuropneumonia. The term mycoplasma (Greek: mykes = fungus and plasma = formed) was first used to describe the pleuropneumonia-like organisms in the 1950s. This designation was initially intended to describe the growth form of *M. mycoides*, but the term soon gained widespread usage and was applied to all pleuropneumonia-like organisms of human and animal origin identified at that time. Over subsequent years, several other human mycoplasmal species were described, and in 1954 Shepard provided the first description of T-strain mycoplasmas, later known as ureaplasmas, when he was able to cultivate them in vitro from the urethras of men with nongonococcal urethritis (258). The pleuropneumonia-like organisms were not fully differentiated from bacterial L forms until the 1960s, when it was finally proven that mycoplasmas were unable to produce cell walls under any circumstances, making them unique among the prokaryotes.

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TABLE 1. Mollicute flora of humans[a]

Organism	Primary site of colonization		Role in human disease[b]
	Respiratory tract	Urogenital tract	
Acholeplasma laidlawii	+	−	No
Mycoplasma amphoriforme	+	−	?
Mycoplasma buccale	+	−	No
Mycoplasma faucium	+	−	No
Mycoplasma fermentans	+	+	Yes?
Mycoplasma genitalium	−	+	Yes
Mycoplasma hominis	−	+	Yes
Mycoplasma lipophilum	+	−	No
Mycoplasma orale	+	−	No
Mycoplasma penetrans	−	+	?
Mycoplasma pirum	?	?	No
Mycoplasma pneumoniae	+	−	Yes
Mycoplasma primatum	+	+	No
Mycoplasma salivarium	+	−	No
Mycoplasma spermatophilum	−	+	No
Ureaplasma parvum	−	+	Yes
Ureaplasma urealyticum	−	+	Yes

[a] Mollicute species listed are those for which humans are presumed to be the primary host. The table does not include occasional isolates likely to be of animal origin that have been recovered from humans on rare occasions.
[b] In immunocompetent persons.

The class *Mollicutes* was established in the 1960s to include the mycoplasmas and related organisms and it now contains four orders, five families, eight genera, and more than 200 known species that have been detected in humans, vertebrate animals, arthropods, and plants. Mollicutes for whom humans are the primary host are listed in Table 1; at least 17 well-documented species are now known to occur, primarily localized in the respiratory or urogenital tracts. Several of these species are considered commensals, but three in the genus *Mycoplasma* are proven pathogens: *M. pneumoniae*, *M. genitalium*, and *M. hominis. M. fermentans* is an organism which may play a role in human disease in some circumstances. Considerable evidence has accumulated in recent years to suggest it may have an etiologic role as an opportunist in persons with human immunodeficiency virus infection and AIDS (8, 9) and a possible association with chronic arthritic conditions (121, 132). Other organisms such as *M. penetrans* appear to have the potential for being human pathogens (28), but no conclusive proof demonstrating this has been offered to date. The most recent human mycoplasmal species to be recognized is *Mycoplasma amphoriforme*, an organism that has been detected in the lower respiratory tract of several immunocompromised persons in association with chronic bronchitis, and investigations are now under way to determine whether a role in human disease can be established with certainty (335). Details of the updated taxonomy of the *Mollicutes* describing their origin from gram-positive ancestors, their phylogenetic relationships with other bacteria, and their biological properties are available in recently published reviews and reference texts (186, 322, 325).

Mycoplasmas represent the smallest self-replicating organisms, in terms of both cellular dimensions and genome size, that are capable of a cell-free existence. Their small genomes and limited biosynthetic abilities are responsible for many of their biological characteristics and requirements for complex growth media for cultivation in vitro. Lack of a rigid cell wall in all members of the class *Mollicutes* prevents them from staining by Gram stain, confers pleomorphism on their cells, and makes them very susceptible to dehydration, thereby limiting them to a parasitic existence in association with eukaryotic cells of their host. Another characteristic of most mollicutes is the requirement for sterols in artificial growth media, supplied by the addition of serum to provide the necessary components of the triple-layered membrane that gives structural support to the osmotically fragile organisms.

Within a few years following the first descriptions and characterization of *Ureaplasma* as a human pathogen implicated in nongonococcal urethritis in 1954, there were reports of a possible association of this organism in adverse pregnancy outcomes and low birth weight in neonates. Since then, additional evidence has accumulated implicating ureaplasmas in infertility, postpartum endometritis, chorioamnionitis, spontaneous abortion, stillbirth, premature birth, perinatal morbidity and mortality, pneumonia, bacteremia, meningitis, and chronic lung disease of prematurity, also known as bronchopulmonary dysplasia (BPD). *M. hominis* has also been implicated in a number of these conditions affecting pregnant women and their offspring.

Many questions remain unanswered about the role of these organisms as human pathogens for a variety of reasons. These include the high prevalence of mycoplasmas in healthy persons; poor design of many of the earlier research studies that attempted to relate the mere presence of these organisms in the lower urogenital tract to pathology in the upper tract or in offspring; failure to consider other multifactorial aspects of some maternal conditions and potential confounders (e.g., bacterial vaginosis); unfamiliarity of clinicians and microbiologists with the complex and fastidious nutritional requirements necessary for in vitro cultivation; and considering these organisms only as a last resort in conditions thought to be most likely due to other microorganisms.

In recent years, detection of several mycoplasmal species in the urogenital tract such as *M. fermentans*, *M. penetrans*, and *M. genitalium* and improved molecular-based detection methods has mandated a reassessment of the possibilities that mycoplasmas and ureaplasmas may be of clinical significance in a variety of urogenital infections affecting pregnant women and neonates, which are the focus of this review. The availability of the complete genome sequence of *Ureaplasma parvum* (96) and *M. genitalium* (87) has greatly improved understanding of their basic biology and pathogenic properties. Unfortunately, the genome of *M. hominis* has not been completely sequenced and annotated as of late 2005, but this project is currently ongoing.

The topic of perinatal mycoplasmal and ureaplasmal infections (collectively referred to as genital mycoplasmas) was last reviewed in *Clinical Microbiology Reviews* in 1993 (47) and that publication provided a broad and extensively detailed discussion current as of that time. The present review is not meant to be all inclusive; nor is it intended to repeat information presented in depth in the earlier publication. Instead, most attention will be focused on the following topics related to the genital mycoplasmas: (i) recent work describing the epidemiology and establishment of these organisms as causes of neonatal infections and premature birth; (ii) current evidence link-

TABLE 2. Diseases in adults associated with or caused by *Mycoplasma hominis*, *Mycoplasma genitalium*, and *Ureaplasma* species[a]

Disease	*Ureaplasma* spp.	*M. hominis*	*M. genitalium*[b]
Male urethritis	+	−	+
Prostatitis	±	−	±
Epididymitis	±	−	−
Urinary calculi	+	−	−
Pyelonephritis	±	+	−
Bacterial vaginosis	±	±	−
Cervicitis	−	−	+
Pelvic inflammatory disease	−	+	+
Infertility	±	−	±
Chorioamnionitis	+	±	−
Spontaneous abortion	+	±	−
Prematurity/low birth weight	+	−	−
Intrauterine growth retardation	±	−	−
Postpartum/postabortion fever	+	+	−
Extragenital disease (including arthritis)	+	+	+

[a] −, no association or causal role demonstrated; +, causal role; ±, significant association and/or strong suggestive evidence, but causal role not proven.
[b] In the case of *M. genitalium*, lack of disease association may reflect the fact that insufficient studies using appropriate detection techniques have been attempted since this mycoplasma is much more fastidious and difficult to detect than *M. hominis* and *Ureaplasma* spp.

ing ureaplasmas and BPD; (iii) recent developments in the taxonomy of the genus *Ureaplasma* and implications for differential pathogenicity of the 2 biovars, now designated as separate species; (iv) the neonatal host response to infection; (v) advances in laboratory detection of mollicutes; and (vi) therapeutic considerations.

MYCOPLASMAL COLONIZATION AND DISEASE IN THE LOWER UROGENITAL TRACT OF ADULTS

In order to understand the potential role of genital mycoplasmas in perinatal and neonatal infections and the reasons why many questions about their significance in these settings remain unanswered, it is necessary to gain an appreciation for the epidemiology of these organisms in adult men and women. *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%. The incidence of each is somewhat lower in the urethra of males. Colonization is linked to younger age, lower socioeconomic status, sexual activity with multiple partners, African-American ethnicity, and oral contraceptive use (47).

There is now ample evidence from clinical studies involving culture, serology, and more recently from PCR assays in humans, and from experimental infection of laboratory animals that these organisms play etiological roles in a variety of urogenital diseases of men and women as summarized in Table 2. For some conditions, such as nongonococcal urethritis for *Ureaplasma* spp., Koch's postulates have been fulfilled and a portion of clinical cases of these entities are known to be caused by these respective organisms (293). However, attempts to link inflammatory diseases of the upper urogenital tract with isolation of the organisms in the lower tract are not always successful, complicating our understanding of their significance as pathogens in many conditions. Thus, the importance of genital mycoplasmas in other urogenital conditions such as bacterial vaginosis and prostatitis remains open to debate. The discrepancy sometimes observed between the presence of genital mycoplasmas in the lower tract and disease in the upper tract is apparently due to the fact that upper tract colonization and disease occurs in only a subpopulation of persons who are colonized in the lower tract and that the reasons and risk factors for such upper tract involvement are unknown (293).

Conditions involving adults that have been associated with or shown to be caused by *M. hominis* and *Ureaplasma* spp. are discussed in more detail elsewhere (129, 283, 284, 293, 311) and will not be dealt with further in this review with the exception of conditions directly related to perinatal and neonatal infections covered in subsequent sections. These organisms may disseminate to other body sites in persons of any age, especially when the immune system is compromised, and are known to cause significant extragenital diseases (92, 195).

MECHANISMS OF PATHOGENESIS

Localization and Cytadherence

The *Mollicutes* are primarily mucosally associated organisms residing in the respiratory or urogenital tracts of their hosts in close association with epithelial cells. In some species, particularly *M. fermentans*, *M. penetrans*, *M. genitalium*, and perhaps even *M. pneumoniae* and *M. hominis* in some cases, invasion of host cells occurs and the organisms reside intracellularly. Such intracellular localization may contribute to the chronicity of infections and their ability to evade the host immune response (23, 44, 63, 286, 325). The cytoskeletal rearrangements, invasions, and receptors involved with mycoplasmal invasion of host cells and their intracellular survival are described thoroughly in Rottem's comprehensive review of this subject (239). It is important to stress that the extent to which *M. hominis* may invade host cells and reside there in vivo has not been determined, even though its ability to enter cultured cells in vitro has been demonstrated (286).

Localization and attachment on host cell surfaces is important in the ability of mycoplasmas to colonize and subsequently produce pathological lesions, even if cellular internalization does not occur. The steps in the assembly of the multiple proteins comprising the attachment organelle, the process of cytadherence, and release of inflammatory mediators that cause damage to the respiratory epithelium are complex and they have been studied intensively for *M. pneumoniae* for more than 20 years (44, 129, 158, 159, 239, 283, 298, 325). Other mycoplasmas such as *M. genitalium*, *M. pirum*, and *M. penetrans* also have a flask-shaped morphology and terminal attachment organelles and knowledge of the cytadherence processes of these mycoplasmas is increasing, due to knowledge gained through study of *M. pneumoniae* cytadherence (23, 129, 230, 239).

Factors involved with the attachment of *M. hominis* and *Ureaplasma* spp. to mucosal surfaces have not been extensively characterized. These mollicutes do not have the prominent attachment tips described in the other species mentioned above, but some investigation has been done in this area. Work by Henrich and colleagues (113) led to the identification and initial characterization of cytadherence proteins in *M. hominis*.

They were able to block adherence of mycoplasmas to HeLa cells using homologous monoclonal antibodies, suggesting that specific proteins may be involved in cytadherence. A major adhesin protein, also known as the variable adherence-associated antigen (Vaa), may undergo antigenic variation and assist *M. hominis* in evasion of host immune defenses (32, 114, 230). The Vaa antigen is expressed in vivo during chronic active arthritis associated with *M. hominis* infection and is highly immunogenic in the human host (346).

Variation of mycoplasmal cell surface protein antigens at a high rate may facilitate their persistence in invasive sites (44, 48, 348). Similar to what has been described for the Vaa antigen in *M. hominis* (32, 114, 230), the MB antigen of *Ureaplasma* spp. undergoes a high rate of size variation in vitro and is variable in size on invasive ureaplasma isolates. Zheng et al. (347) reported that the MB antigen of *Ureaplasma* spp. contains serovar-specific and cross-reactive epitopes and is a predominant antigen recognized during human infections.

Ureaplasmas are known to adhere to a variety of human cells including erythrocytes (243), spermatozoa (41), and urethral epithelial cells (260). Ureaplasmas bind spontaneously to neutrophils and directly activate the first component of complement (288, 334). *Ureaplasma* adhesins are proteins expressed on the surface of the bacterial cell. There may be several of them involved in the cytadherence process, which has not yet been characterized in its entirety (243, 262). Pretreatment of HeLa cell monolayers or human erythrocytes with neuraminidase will reduce ureaplasmal adherence, suggesting that the receptors for ureaplasma adhesins are sialyl residues and/or sulfated compounds, similar to what has been observed with *M. pneumoniae* and other mycoplasmas (325).

Secretory Products

Arginine metabolism by *M. hominis* and urease activity in ureaplasmas have been suggested as potential virulence factors. More than 40 years ago Schimke and Barile (255) proposed that *M. hominis* generates ATP by hydrolysis of arginine, a process that utilizes a three-enzyme pathway with end products of CO_2 and NH_3. Release of NH_3 in large amounts may deplete arginine in vitro, resulting in a cytotoxic effect (44, 230). However, direct evidence that arginine depletion by *M. hominis* causes toxic effects in vivo is still lacking. Release of NH_3 also occurs in *Ureaplasma* spp. through hydrolysis of urea mediated by a very potent urease. Hydrolysis of urea is the predominant means by which these organisms generate ATP, making them unique in the class *Mollicutes* in this respect (261). Release of NH_3 in the urinary tract can cause elevation of urinary pH and precipitation of magnesium ammonium phosphate, also known as struvite. Inoculation of ureaplasmas into rat bladders results in the formation of struvite stones (105).

Clinically, *Ureaplasma* spp. have been cultured directly from renal stones, and these organisms have been isolated from voided urine in 31 of 247 patients (13%) with metabolic stones, compared to 43 of 145 patients (30%) with infection stones ($P < 0.001$). In the patients for whom stone cultures were performed, ureaplasmas were found in 2 of 125 patients (2%) with metabolic stones, compared to 10 of 64 patients (16%) with struvite stones ($P < 0.001$). These observations strongly suggest that *Ureaplasma* spp. are linked to the formation of infection stones in the urinary tract, mediated by urease activity (105). The potential pathogenic effect of ureaplasmal urease and its NH_3 metabolic by-product was demonstrated in a mouse model by Ligon et al. (170) in which they were able to demonstrate toxicity of ureaplasmas injected intravenously that was prevented by injection of fluofamide, a potent urease inhibitor.

Information gained through study of the *Ureaplasma* genome has produced some interesting, albeit somewhat unexpected, findings regarding other potential virulence factors (96). Immunoglobulin (Ig) A1 protease activity was first described in *Ureaplasma* spp. more than 20 years ago using radiolabeled IgA and was shown to be present in all 14 serotypes and 34 of 35 wild-type strains (237). This serine protease has been examined and characterized further in additional studies. Five ureaplasma clinical isolates obtained from urine, cervix, vagina, amniotic fluid, and synovial fluid along with 13 serotypes were shown to be positive for IgA1 protease activity by Kilian and coworkers (144). Kapatais-Zoumbos et al. reported IgA1 protease activity in 28 isolates of *Ureaplasma* spp. and speculated that this enzyme may play a role in host specificity in facilitating mucosal colonization since ureaplasmas from nonhuman hosts could not cleave human IgA and human strains could not cleave murine, porcine, or canine IgA (138). This enzyme has therefore been documented in most ureaplasmal strains tested thus far, but it is absent in *M. hominis*, *M. fermentans*, and *M. pneumoniae* (138, 144, 145, 266).

Since IgA is the predominant immunoglobulin secreted at mucosal surfaces, IgA proteases may facilitate colonization by microorganisms by degrading this important component of the mucosal immune system. However, Robertson et al. (237) emphasized that IgA1 protease may not be a significant virulence factor in ureaplasmas because they were able to detect its presence in men with nongonococcal urethritis and with strains isolated from healthy persons. Glass et al. (96) could not identify the gene for IgA1 protease in the genome of *U. parvum* serotype 3. They speculated that the ureaplasma enzyme may have diverged so far from orthologues in other bacteria they were unrecognizable, or they may have convergently evolved an enzyme with no recognizable similarity to other enzymes. Even though most of the clinical isolates of *Ureaplasma* spp. evaluated in the studies cited above demonstrated IgA1 protease activity, the extent to which individual ureaplasma strains may lack functional activity of this enzyme is not known.

The presence of phospholipases A and C in *Ureaplasma* spp. has been suggested to be the means by which ureaplasmas may initiate preterm labor by liberating arachidonic acid and altering prostaglandin synthesis (69–71). Support for this hypothesis comes from studies that have demonstrated significant elevations of phospholipase A2 in serum and amniotic fluid specimens from women in preterm labor with chorioamnionitis than those undergoing term labor (157). De Silva and Quinn (69–71) identified and characterized phospholipase activities in multiple ureaplasma serotypes and reported that the specific activities of phospholipase A2 differed according to serotype, while the activities of phospholipases A1 and C were similar. They speculated that differences in phospholipase activity might cause differences in pathogenic potential for the various serotypes in terms of adverse pregnancy outcomes. However,

Glass and colleagues (96) were unable to identify phospholipase activity in the serotype 3 ureaplasma strain for which the complete genome was sequenced and gave the same possible explanations as those for the apparent lack of IgA1 protease activity. Interestingly, Walther et al. (328) were unable to demonstrate phospholipase activity in *M. hominis* and they were also unable to detect phospholipase A2 coding sequences in DNA analysis (271). These findings suggest *M. hominis* is not important in the initiation of premature labor through elaboration of phospholipases and stimulation of prostaglandin activity.

The hemolytic activity of *M. pneumoniae* is due to production of H_2O_2 and is inhibited by catalase (264). In contrast, the hemolytic activity of ureaplasmas is not inhibited by catalase, suggesting an alternative enzyme system may be responsible (96). Glass et al. (96) reported that *Ureaplasma parvum* has two hemolysins, encoded by the *hlyC* and *hlyA* genes. Since *hlyC* has an orthologue in *M. pneumoniae*, in which hemolysis is mediated by H_2O_2, *hlyA* may function as a virulence factor in *Ureaplasma* spp. (96). Supporting evidence for this concept lies in the fact that orthologues of the hemolysin *hlyA* mediate hemolytic and cytotoxic activity in other microbes and some mycobacteria which lack this gene are nonpathogenic (96). Antimicrobial resistance as a virulence factor in genital mycoplasmas is discussed in a subsequent section.

EFFECT ON INFERTILITY AND PREGNANCY OUTCOME

Infertility

The possible role of genital mycoplasmas in diseases of the female reproductive tract that affect pregnancy outcome or lead to infertility has been debated since the 1970s, and there are still no clear answers to the many questions that remain. The initial associations with infertility came following reports that ureaplasmas could be isolated from the lower genital tract more commonly in infertile couples than in fertile couples, but this has not been found consistently in subsequent investigations (97, 193, 303). Additional studies that have utilized cultures from endometrial tissue obtained at laparoscopy have also shown that ureaplasmas can be recovered more commonly from infertile women than from fertile women, even when cervicovaginal isolation rates from the two groups are similar (273, 274). Ureaplasmas are known to attach to sperm and decrease motility, explaining the association with male factor infertility seen in some studies (284). Elimination of ureaplasmas by antimicrobial treatment has been correlated with improvement in sperm motility, quantity, and appearance by some investigators (275, 296). However, it has been stressed that the drugs used to treat ureaplasmas, such as tetracyclines, have broad-spectrum activities that can affect other microbes (280, 284). Conception rates following antimicrobial treatment of infertile couples also vary, as reviewed elsewhere (284). Most work in this area was performed during the 1980s or earlier, with little activity in recent years. Overall, there seems to be little enthusiasm for concluding that *Ureaplasma* spp. or *M. hominis* plays an important role in infertility.

Postpartum Endometritis

One of the first conditions affecting pregnancy that was ascribed to genital mycoplasmas was their role in postpartum endometritis. The first studies that attempted to correlate genital mycoplasmas with postpartum endometritis were based on cervicovaginal cultures and caused much confusion with their inconclusive results (42). However, both *M. hominis* and *Ureaplasma* spp. can be detected in the bloodstream of some women with postpartum or postabortion fever, with *M. hominis* being more common. This condition is usually self-limiting, but in some cases in which *M. hominis* is involved, dissemination to joints, resulting in arthritis, may occur. This topic has been reviewed in detail elsewhere (44, 284). Chorioamniotic colonization with *Ureaplasma* spp. was associated with a threefold increased risk of post-Cesarean delivery endometritis and an eightfold higher risk in women in whom the onset of labor was spontaneous (17).

The same investigators later provided indirect evidence that ureaplasmas may be involved in post-Cesarean delivery endometritis in a study in which 301 women who received doxycycline plus azithromycin were compared to 297 who received a placebo (16). The interesting finding in that investigation was that prophylaxis with antibiotics having activity against ureaplasmas reduced the length of hospitalization, frequency of endometritis, and wound infections. A recent study from Israel (51) detected no difference in prevalence of *Ureaplasma* spp. in cervicovaginal swabs of women with and without postpartum endometritis, but they were able to detect a difference quantitatively in that more than twice as many women with endometritis had high numbers ($>10^5$ CFU) of organisms detected, suggesting an etiological association. To our knowledge, no studies have been performed that have specifically evaluated the role of *M. genitalium* in postpartum or postabortion fever and endometritis.

Chorioamnionitis, Spontaneous Abortion, and Preterm Labor

The importance of genital mycoplasmas in prematurity, pregnancy loss, and chorioamnionitis have been topics of great interest in recent years and, like several others, have not been satisfactorily resolved. Analyses have been complicated by different study designs, inappropriate sampling sites, and failure to adjust for many potentially confounding factors. Nonetheless, investigation is continuing. Earlier work that provided an important basis on which more recent studies have been developed has been reviewed in detail (44, 47). Studies that were limited to sampling the lower genital tract of women have yielded inconclusive results, mainly because not all women who are colonized in the lower tract will develop infection in the upper tract.

Isolation of *Ureaplasma* spp. but not *M. hominis* from the chorioamnion has been consistently associated with histological chorioamnionitis and is inversely related to birth weight, even when adjusting for duration of labor, rupture of fetal membranes, and presence of other bacteria (44, 47). These organisms can invade the amniotic cavity and persist for several weeks when fetal membranes are intact and initiate an intense inflammatory reaction in the absence of labor (43, 85,

103). Moreover, ureaplasmas can then be isolated from the chorioamnion and detected in inflamed areas by immunofluorescence (46). Even though these conditions may be clinically silent, these findings are strongly supportive of a causal role for *Ureaplasma* spp. in chorioamnionitis.

M. hominis rarely seems to invade the chorioamnion and amniotic fluid in the absence of other microorganisms, and data to support an independent role for this mycoplasma in either histological or clinical amnionitis are modest at best. The extent to which the genital mycoplasmas may produce clinical amnionitis is unclear. As discussed above, both can be detected in endometrial tissue and cause postpartum or postabortion fever, sometimes accompanied by bacteremia. Isolation rates of *Ureaplasma* spp. and *M. hominis* in symptomatic and asymptomatic women have been similar, but symptomatic women were more likely to develop a serum antibody response (44).

Intrauterine infection is a major cause of preterm labor and can be detected in approximately half of all preterm births, especially those occurring at less than 30 weeks of gestation. Such infections are often subclinical (148). The earlier the gestational age at delivery, the higher the frequency of intraamniotic infection (98). This relationship is believed to be related to the concept that uterine contractions may be induced by phospholipases produced by microorganisms, as well as cytokines (190). Cytokines elaborated in the amniotic fluid in response to the presence of microorganisms trigger prostaglandin synthesis in the amnion, chorion, decidua, and myometrium, leading to uterine contractions, cervical dilatation, membrane exposure, and greater entry into the uterine cavity (148).

Vaginal carriage of *Ureaplasma* spp. is not reliably predictive of preterm labor (42), but there is an association when it is present in the amniotic fluid or placenta (43, 125, 163, 339, 342). Two recent reviews of antibiotic trials involving treatment of pregnant women who were culture positive for ureaplasmas in their vaginas concluded that there is insufficient evidence to recommend administration of antibiotics to women with ureaplasmas in the vagina to prevent preterm birth (148, 229). *M. hominis* and *Ureaplasma* spp. can be isolated from endometrial tissue of healthy, nonpregnant women, indicating that they may be present at the time of implantation and might therefore be involved in early pregnancy losses (44). Horowitz et al. (122) reported that women whose cervices were culture positive for *Ureaplasma* spp. and who had a high level of antibody against ureaplasmas were more likely to develop pregnancy complications than women with a negative culture and absence of antibodies. These investigators also reported that women with amniotic fluids that were culture positive for *Ureaplasma* spp. and who had elevated antibodies were more likely to experience complications including preterm labor, low birth weight, and fetal death than women without antibody against ureaplasmas (124). In view of the fact that accurate methods for measuring antibody against ureaplasmas are not widely available outside of specialized research laboratories, these findings may not have direct clinical relevance at present, but they are interesting nonetheless.

Studies of women from whom ureaplasmas and *M. hominis* were isolated from the endometrium or placenta have shown a consistent association with spontaneous abortion, but this has not proven true for studies limited to sampling the lower genital tract (293). Joste et al. (136) reported that ureaplasma cultures were positive in 11 of 42 (26%) early spontaneous abortions versus 0 of 21 elective abortions. Other circumstantial evidence linking ureaplasmas with spontaneous abortion, low birth weight, intrauterine growth retardation, and preterm labor includes reports of successful pregnancies following antimicrobial treatment and serological studies (44). Underlying problems that complicate a complete understanding of any potential role for genital mycoplasmas in low birth weight are that *M. hominis* and to a lesser extent *Ureaplasma* spp. can be components of the varied flora that occur with bacterial vaginosis, a condition associated with low birth weight (79, 119, 190), and problems in experimental design of studies including failure to consider potential roles for organisms other than mycoplasmas and ureaplasmas or use of control groups of questionable comparability.

Isolation of *Ureaplasma* spp. in pure culture from amniotic fluid obtained from women with intact fetal membranes who subsequently experienced fetal loss in the presence of histological chorioamnionitis has been documented by multiple investigators, indicating that in some cases this organism has a causal role in spontaneous abortion (43, 85, 103). Support for use of PCR to detect ureaplasmas was presented in a recent investigation which determined that patients with a positive PCR for *Ureaplasma* spp. but a negative amniotic fluid culture had a higher rate of significant neonatal morbidity than those with a negative culture and negative PCR ($P < 0.05$). However, no significant differences in perinatal outcome were observed between patients with a negative culture but positive PCR and those with a positive amniotic fluid culture (342). Another recent study (93) found that preterm labor occurred in 58.6% women with a positive PCR assay for ureaplasmas at 15 to 17 weeks of gestation compared with only 4.4% of women with negative PCR results, suggesting the potential value of PCR testing of second trimester amniotic fluid to identify women at risk for preterm labor and delivery.

Patients with preterm premature rupture of membranes and microbial invasion of the amniotic cavity with *Ureaplasma* spp. experience a robust host inflammatory response in the fetal, amniotic, and maternal compartments (343). Abele-Horn et al. (4) suggested that the density of ureaplasmal colonization is a factor that correlates with adverse pregnancy outcome, including development of chorioamnionitis and preterm delivery. Logistic regression analyses of demographic and obstetric variables indicate that the presence of *U. urealyticum* alone or with other bacteria in the chorioamnion is independently associated with birth at <37 weeks of gestation regardless of the duration of labor (44). While the association between ureaplasmal chorioamnion infection and premature birth is strong, this association does not prove a cause-and-effect relationship.

Treatment of pregnant women colonized with *Ureaplasma* spp. with erythromycin or placebo has shown no significant differences in infant birth weight or gestational age at delivery, frequency of premature rupture of membranes, or neonatal outcome (83). On the basis of current evidence, one might have predicted failure of this trial. First, if *Ureaplasma* is involved in premature birth, it probably produces an effect via intrauterine infection. If only subgroups of pregnant women are at risk, then it is unlikely that a prospective study based on

cervical colonization will show an association. Another major consideration is that no information concerning the efficacy of erythromycin for treating intrauterine infections is available. Erythromycin does not effectively penetrate the amniotic sac nor does it eradicate ureaplasmas from the cervix and vagina, probably because of the normally low vaginal pH. Perhaps a more important reason the treatment trial failed is that the majority of women in this study were treated starting at or beyond week 29 of gestation. It is possible that treatment earlier in pregnancy would have been more effective in preventing invasion of the fetal membranes.

Isolation rates of *Ureaplasma* spp. from the chorioamnion are higher in infants who weigh <1,500 g at birth and are born before 32 weeks of gestation. Since only 1% of women deliver neonates weighing <1,500 g at birth, a very large number of women would have had to be treated to demonstrate a measurable effect. Two recent reviews of published antibiotic trials involving treatment of pregnant women who were culture positive for ureaplasmas in their vaginas concluded that there is insufficient evidence to recommend administration of antibiotics to women with ureaplasmas in the vagina to prevent preterm birth (148, 229). A detailed review of data relating to the role of genital mycoplasmas in preterm birth through the 1990s has been published elsewhere (44).

Bacterial Vaginosis

The first reported association of genital mycoplasmas with vaginitis occurred over 40 years ago. Since that time some evidence has accumulated that *M. hominis* may be of significance in the condition now known as bacterial vaginosis (BV). Symptomatic BV is characterized in part by a watery discharge with a fishy odor, but half of the women with this infection may be asymptomatic or experience only mild symptoms. Women with BV consistently have an increased prevalence of *Gardnerella vaginalis*, selected anaerobic bacteria, and *M. hominis* along with a decreased prevalence of lactobacilli (83, 190, 191, 242). *M. hominis* may act symbiotically with other BV-associated bacteria or as the sole pathogen (291, 292) based on the observation that this mycoplasma can be found in large numbers in the vagina of most women with BV but less often in healthy women. When present in healthy women, it is usually there in much lower numbers than in women with BV (117, 141).

It is apparent that no single organism causes BV, but an independent association has been found between BV and four groups of vaginal bacteria: *G. vaginalis*, *Mobiluncus* spp., anaerobic gram-negative rods, and *M. hominis* (117). However, the exact role and significance of *M. hominis* in BV remain uncertain, as other studies have yielded conflicting results. In one study, eradication of *G. vaginalis* with metronidazole, a drug inactive against *M. hominis*, cleared nonspecific vaginitis (now known as BV), whereas eradication of *M. hominis* alone with doxycycline did not, raising doubts over its role in this condition (217). Conversely, relapse of BV after treatment with metronidazole has been attributed to its lack of activity against *M. hominis* (66), but if the other organisms are eliminated, *M. hominis* may also disappear. Arya et al. (18) found no role for *M. hominis* in the epidemiology of BV in a study of 341 women who harbored the organism in their vaginas, while Keane and colleagues (141) detected no difference in the occurrence of *M. genitalium* and *Ureaplasma* spp. in women with or without BV, but found *M. hominis* significantly more often in women with BV. In contrast, another study isolated *M. hominis* and *Ureaplasma* spp. from 17% and 53%, respectively, of women with BV, versus 2% and 13%, respectively, of controls (50). A study using PCR for detection of microorganisms found *M. hominis* at much lower frequencies than *G. vaginalis* and found no difference in the frequency of its detection in women with or without BV (345). Although *Ureaplasma* spp. may not be independently associated with BV, the prevalence of vaginal colonization by ureaplasmas may be increased about twofold, and the intravaginal concentration of these organisms may be increased 100-fold (102).

BV occurs in 15 to 20% of pregnant women (190, 191) and this condition has been associated with premature birth. However, the precise relationship among BV, ureaplasmas, and preterm birth is not known. Some have postulated that the increased intravaginal concentrations of BV organisms may result in increases in the synthesis of phospholipase A2 and the production of prostaglandins, which may lead to preterm labor or premature rupture of membranes (83, 190). Alternatively (83, 190) *Bacteroides* spp. in the lower genital tract could produce enough proteases to weaken the fetal membrane strength, causing premature rupture of membranes and invasion by other organisms. In addition, it is possible that certain BV-associated microorganisms may be more likely to invade the amniotic sac simply because these organisms are present in larger numbers. However, the latter possibility cannot be the total explanation for the association of ureaplasmas with prematurity, since intravaginal concentrations of *Peptococcus* spp. are also increased in women with BV but are found infrequently in the chorioamnion and amniotic fluid (83, 118, 190, 191, 265).

The presence of BV is independently and significantly associated with birth at <37 weeks of gestation when cervical organisms and obstetric and demographic factors are taken into consideration (118). However, these studies have not determined whether BV is associated with premature delivery independently of chorioamnion infection (with either organisms associated with BV or those that are not). Hillier et al. (118) performed multiple logistic regression to determine the strength of the relation between the recovery of any organism from the chorioamnion and BV. After adjustment for factors related to both BV and the recovery of organisms from the chorioamnion, BV was significantly associated with the isolation of organisms from the chorioamnion. Due to the small numbers of patients it was not possible to determine the effect of individual organisms, to address the question of whether BV is associated with premature delivery independently of chorioamnion infection, or to determine whether chorioamnion infection by *Ureaplasma* spp. occurred independently of BV.

VERTICAL TRANSMISSION

Interest in the epidemiology of genital mycoplasma infections in infants began more than 30 years ago, when the association was made that colonization of newborn infants was inversely related to birth weight (35, 86, 147). Now it is understood that *Ureaplasma* spp. and *M. hominis* can be transmitted

from an infected females to the fetus or neonate by at least three different routes (316). First, there can be an ascending intrauterine infection in which the organisms gain access to the amniotic sac, where they multiply and are then passed into the fetal lung. This can occur early in pregnancy, even when fetal membranes are intact, and infection can persist for several weeks. Fetal acquisition of these organisms can also occur through a hematogenous route through placental infection through involvement of the umbilical vessels. *Ureaplasma* spp. have been isolated directly from maternal and umbilical cord blood at the time of delivery (142). Intrauterine infection with *Ureaplasma* spp. can result in chorioamnionitis, dissemination to fetal organs, and congenital pneumonia (43). Finally, acquisition of these organisms by the neonate can occur through passage of an infected maternal birth canal with resultant colonization of the skin, mucosal membranes and respiratory tract. Ureaplasmas can be isolated from the endotracheal secretions in up to 40% of newborn infants within 30 min to 24 h after birth (45, 128, 207).

Rates of transmission of ureaplasmas from mother to offspring have been the subject of several studies. The isolation of ureaplasmas from neonates will reflect the frequency of maternal colonization in the lower urogenital tract of women in the population studied. Vertical transmission of *Ureaplasma* spp. has been reported to range from 18 to 88% and isolation rates vary inversely with gestational age, according to most studies (52, 77, 137, 248, 276). Kafetzis et al. (137) recently demonstrated a vertical transmission rate of 60% for infants with a birth weight of ≤1,000 g versus only 15.3% for infants with birth weights of ≥1,500 g. These investigators also found that the overall ureaplasma colonization rate was 10% for full-term infants versus 24% of preterm infants. Records from the Diagnostic Mycoplasma Laboratory at the University of Alabama at Birmingham show that *Ureaplasma* spp. alone were detected in 56 of 307 (18%) sequential endotracheal aspirates cultured from preterm neonates with respiratory distress. *Ureaplasma* spp. in combination with *M. hominis* occurred in 27 specimens (9%) and *M. hominis* alone was identified in 16 specimens (5%). Some investigators have noted that specimens collected on the day of birth for detection of ureaplasmas may not be positive, but subsequent specimens may eventually demonstrate their presence. Bowman and coworkers cultured endotracheal aspirates twice weekly on preterm neonates undergoing mechanical ventilation and determined the average age for a positive culture was 8 days, but some were not positive until the third week or later, perhaps due to a very low initial inoculum (34).

Despite the likelihood that women who are colonized with genital mycoplasmas will transmit them to their offspring, the mere presence of these organisms in surface cultures of neonates is not evidence of pathogenicity. Although the presence of *Ureaplasma* spp. has been documented for long periods in the lower respiratory tract of preterm infants (45), surface colonization of full-term infants tends to be transient and declines beyond 3 months of age (86). Recolonization of the lower urogenital tract may occur following puberty and when sexual activity is initiated, or if there is sexual abuse (313). However, genital mycoplasmas may occasionally be isolated from the vagina of healthy prepubescent girls (107).

RESPIRATORY DISEASES IN INFANTS

Congenital and Neonatal Pneumonia

Respiratory disease remains the most common cause of perinatal morbidity and mortality, especially in preterm infants, despite many advances in neonatal intensive care and resuscitation, and the introduction of artificial surfactant in the early 1990s. Some of the earliest investigations suggestive of a potential role for *Ureaplasma* spp. in neonatal respiratory disease came in the mid-1970s, when Tafari et al. (277) described the isolation of these organisms from lungs of stillborn infants with pneumonitis. Case reports and prospective studies performed during the 1980s and 1990s have shown conclusively that *Ureaplasma* spp. can cause respiratory disease in newborn infants in some circumstances.

Evidence that *Ureaplasma* spp. are a cause of congenital pneumonia includes: isolation of the organism in pure culture from amniotic fluid; the affected lungs of neonates less than 14 h after birth, and from the chorioamnion (43, 85); demonstration of a specific IgM response in the neonate (225); presence of histological pneumonia and chorioamnionitis in culture-positive neonates and placentas (43, 46, 103, 318); clinical manifestations of respiratory distress in culture-positive infants (45, 204, 318); radiographic changes indicative of pneumonia in culture-positive infants (60, 209); demonstration of the organisms in lung tissue by immunofluorescence (46); electron microscopy (225); and development of rodent (240, 308) and primate (326, 338) models of pneumonia that resemble disease in humans. Although individual case reports suggest *M. hominis* may cause pneumonia in newborns, it has not been implicated as a common cause in prospective studies (44).

It is not necessary to reiterate all of the details of case reports and retrospective and prospective studies proving ureaplasmas can cause congenital and neonatal pneumonias that have been reviewed by Cassell et al. (47). However, additional supportive data have been forthcoming during the last few years since this topic was last addressed.

The ability of ureaplasmas to incite an inflammatory response in the bloodstream and lower respiratory tract of neonates has been investigated in an attempt to characterize how these organisms can produce pathological lesions when they gain access to the lung. Ohlsson and coworkers (202) observed an elevation in the peripheral leukocyte count, predominantly in the neutrophil component, in preterm infants from whom *Ureaplasma* spp. were isolated from the lower respiratory tract. Panero et al. (212) correlated isolation of *Ureaplasma* spp. in pure culture from endotracheal aspirates and/or blood in preterm neonates with total leukocyte counts and radiographic evidence of pneumonia. They determined that *Ureaplasma*-positive infants had higher mean total leukocyte counts, absolute neutrophil counts, and band form counts, and greater frequency of pneumonia than infants who were culturally negative.

Additional support for the inflammatory potential for ureaplasmas in preterm neonates was provided by Ollikainen et al. (204), who noted that 11 preterm neonates studied within 12 h of birth who were culturally positive for *Ureaplasma* spp. in the nasopharynx, trachea, and/or bloodstream had significantly higher peripheral leukocyte counts on the first and second days

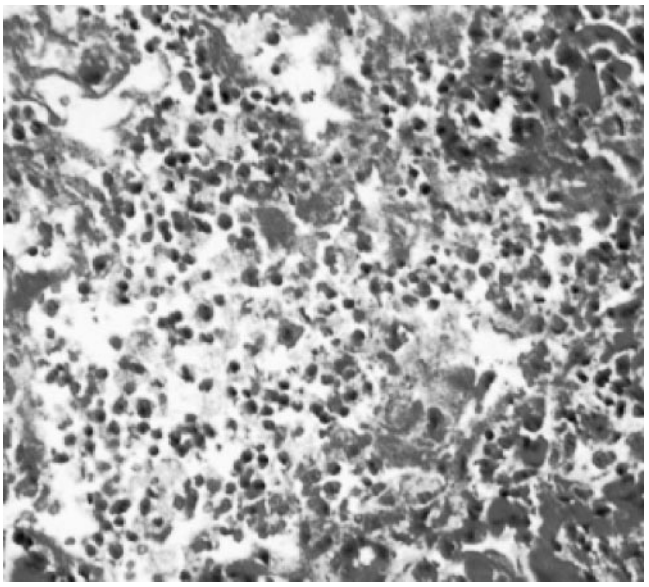

FIG. 1. Photomicrograph of lung (magnification 100×) collected at autopsy of a neonate who died at 6 days of age with pneumonia and sepsis due to *Ureaplasma* spp. (318). Antemortem cultures of blood, pleural fluid, and tracheal secretions and postmortem cultures of nasopharynx, conjunctiva, and brain were positive for *Ureaplasma* spp. in pure culture. There is extensive pneumonitis, mixed mononuclear and polymorphonuclear infiltrate with abundant macrophages, and fibrin deposition.

of postnatal life and more often needed high-frequency oscillatory ventilation than 67 neonates who were culturally negative. Horowitz et al. (123) reported that infants from whom ureaplasmas are isolated from endotracheal aspirates within the first 24 h following delivery were more likely to have neutrophils in their tracheal secretions on day 2 than those who are not colonized. In addition to their contribution to the pathological events in acute pneumonitis, increased numbers of neutrophils in the airways are components of chronic inflammatory lung conditions such as BPD, as discussed in subsequent sections. Figure 1 is a photomicrograph of lung tissue collected from autopsy from a neonate who died with pneumonia and sepsis caused by *Ureaplasma* spp. (318). The tissue reaction shows an extensive and severe inflammatory response with abundant fibrin deposition.

Pneumonia and Other Respiratory Diseases in Older Infants and Children

No convincing evidence exists to support a significant role for *Ureaplasma* spp. or *M. hominis* as common independent causes of pneumonia in otherwise healthy infants beyond the neonatal period, although several investigations have been performed to determine whether these microorganisms might be important in this setting. Stagno et al. (267) performed a microbiologic study of 125 infants aged 2 to 12 weeks who were hospitalized with respiratory syndromes. Infants with chronic lung conditions or acute bacterial pneumonias were excluded. Although the cervicovaginal isolation rate did not differ between mothers of the subjects and those of the controls, ureaplasmas were isolated significantly more often from nasopharyngeal aspirates of infants with pneumonitis than from those of controls, while *M. hominis* was isolated from comparable numbers of infants in each group. However, the majority of ureaplasmal isolates were associated with other organisms, which makes their role, if any, in clinical pneumonitis in this population unclear.

Mere isolation from the upper respiratory tract may not accurately reflect the flora of the lower respiratory tract. Syrogiannopoulos et al. (276) studied 108 full-term infants who were colonized with *Ureaplasma* spp. at birth. They were unable to demonstrate an increased risk of lower respiratory illness during the first 3 months of postnatal life in ureaplasma-colonized infants compared with infants who did not have pharyngeal ureaplasmal colonization. Matlow and coworkers (192) performed a retrospective microbiological evaluation of respiratory tract specimens including lung tissue, bronchoalveolar lavage, lung and endotracheal aspirates, and sputum, nasopharyngeal, and throat specimens obtained from infants and children with various lower respiratory tract diseases. Among 347 specimens, there were 26 culturally positive for *Ureaplasma* spp. Among 278 nonneonatal specimens, only 5 (1.8%) were positive for ureaplasmas. Four of these five isolates were detected in cultures from either bronchoalveolar lavages or endotracheal aspirates, and other pulmonary pathogens were present simultaneously. They concluded that ureaplasmas are infrequently encountered as agents of respiratory disease beyond the neonatal period and routine culture for them is not recommended.

Davies et al. (65) tested infants under 6 months of age who were hospitalized with an admitting diagnosis of pneumonia, proven radiologically, and compared the microbiological results for a variety of bacterial and viral pathogens with those for infants hospitalized with bronchiolitis. They evaluated the presence of ureaplasmas by culture of nasopharyngeal secretions and found that 4 of 46 (8.7%) of those with pneumonia versus 4 of 66 (6.1%) with bronchiolitis were culture positive for these organisms. In three cases *Ureaplasma* spp. occurred simultaneously with *Chlamydia trachomatis* and/or respiratory viruses. It is difficult to make broad conclusions from this study since the authors were making assumptions regarding infection in the lower respiratory tract based on nasopharyngeal cultures and the culture methods that were described did not include agar media specifically designed and proven to support growth of ureaplasmas. These investigators did not detect *M. hominis* in any of the nasopharyngeal specimens, which is consistent with findings of other prospective studies, even though a few cases of pneumonia in infants have been reported to be caused by this mycoplasma (44).

Very little information exists to indicate what the long-term consequences may be from neonatal infection by *Ureaplasma* spp. or *M. hominis* beyond the period of infancy. This problem is confounded by the fact that most neonates with clinically significant respiratory, bloodstream, and/or cerebrospinal fluid infection with these organisms are born preterm and are therefore at much higher risk for long-term sequelae unrelated to the presence of these microorganisms. Ollikainen et al. (203) determined that 22 infants from whom *Ureaplasma* spp. were detected in blood experienced significantly more hospital stays and remained hospitalized for more days during the first 12 months of postnatal life than 18 infants without infection (546

days versus 188 days) and noted that the differences observed were related to an increase in respiratory tract disease among the infants who were culturally positive for *Ureaplasma* spp. These findings most likely represent the greater occurrence of long-term respiratory dysfunction among infants colonized with ureaplasmas. Ureaplasmas are also known to cause lower respiratory infections in immunocompromised children and those receiving therapy for malignancies, but these conditions are not known to be associated with the presence of these organisms in the neonatal period (39, 92, 288).

In recent years, considerable attention has been given to the potential role of *M. pneumoniae* as a cofactor in development or exacerbation of asthma as summarized by Waites and Talkington (325). There is also some recent evidence that colonization or infection of the lower respiratory tract of infants with ureaplasmas may lead to somewhat similar outcomes (25, 161). A Danish study (25) involving 2,927 women determined that maternal vaginal colonization with *Ureaplasma* spp. during pregnancy was associated with infant wheezing (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.2 to 3.6), but not with asthma, during the fifth year of life.

Association of *Ureaplasma* spp. with Development of Chronic Lung Disease in Preterm Neonates

The inflammatory potential of *Ureaplasma* spp. in the mammalian respiratory tract was proven by Rudd et al. (240) by intranasal inoculation of mice with ureaplasma strains that had been originally derived from the lower respiratory tract of preterm neonates. Pneumonia histologically similar to what has been observed in human neonates (318) was reproduced in the mice. This study also showed that newborn mice were more susceptible to colonization of the lower respiratory tract than 14-day-old mice, analogous to what has been observed in humans in that preterm neonates are more susceptible to colonization and disease caused by ureaplasmas than their full-term counterparts.

Viscardi et al. (308) continued work in this area and adapted one of the same murine strains used by Rudd (240) to a juvenile mouse model of ureaplasmal pneumonia. Through this model they were able to characterize an acute and a chronic phase of infection. Pathological effects attributed to the ureaplasmas included focal loss of ciliated respiratory epithelium and increased interstitial neutrophilic infiltrates, presumably due to ureaplasmal adherence and local release of toxic substances such as NH_3 and H_2O_2. The ability of ureaplasmas to adhere to the alveolar epithelial cells of neonatal mice using in situ DNA hybridization was demonstrated by Benstein et al. (26). It is noteworthy that evidence of ureaplasmal infection can be demonstrated in lung tissue by in situ hybridization or culture even when tracheal cultures are negative (27, 327).

Additional information regarding the pathogenicity of ureaplasmas in the neonatal lung was obtained by Walsh et al. (326) through intratracheal inoculation of ureaplasmas into premature baboons delivered by cesarean section. These animals were maintained on 100% oxygen and mechanically ventilated for 6 days. Two animals inoculated with ureaplasmas developed acute bronchiolitis with epithelial ulceration and neutrophil infiltrates, similar to what has been described in ureaplasmal pneumonia in human neonates (225, 318). These lesions were absent in four control animals who were not inoculated with ureaplasmas, but were treated in the same manner otherwise. *Ureaplasma* spp. were recovered in culture from multiple sites in both infected animals including blood, tracheal aspirates, nasopharynges, pleural fluid, lung, and/or kidney tissue, indicating the organisms were replicating in this primate host.

Yoder et al. (338) expanded the preterm neonatal primate model of ureaplasmal infection by inoculating 10 pregnant baboons intra-amniotically with *U. parvum* (serovar 1) and studied the offspring that were delivered electively by cesarean section 48 to 72 h later in comparison to animals that were not exposed to intra-amniotic infection with *U. parvum*. Infant baboons were treated with artificial surfactant, mechanical ventilation and given supplemental oxygen for 14 days until necropsy. Tests for the presence of ureaplasmas and determination of cytokine levels were performed periodically during that time. Experimental findings showed that preterm baboon infants with 48 to 72 h of intra-amniotic exposure to *U. parvum* had early elevations of tracheal cytokines and leukocytes. Their clinical and radiographic features were consistent with acute pneumonitis. Animals that failed to clear *U. parvum* from the lower respiratory tract within the first week had greater risk of lung dysfunction and injury than those who eradicated the organisms, similar to what has been observed in human neonates (49). Histopathological examination of the lungs in the infected animals showed more severe bronchiolitis and interstitial pneumonitis compared with uninfected controls. These findings emphasize the importance of the maternal-fetal immunologic response in the outcome of intrauterine ureaplasmal infections.

Three independent reports associating the presence of *Ureaplasma* spp. in the lower respiratory tracts with progression to BPD, and even death in very low birth weight infants were published in 1988 (45, 247, 329). These studies have stimulated a great deal of additional work in this area in an attempt to understand the true role of these organisms in this clinically important condition. To appreciate why microbial infection may predispose a preterm infant to develop long-term respiratory dysfunction, it is first important to review what is known about the pathophysiology of BPD and the inflammatory potential of microorganisms such as ureaplasmas in the neonatal lung that may be contributory.

Smaller, more immature neonates survive today due to advances in supportive care and mechanical ventilation (165). The increased survival of these vulnerable newborns results in more infants at risk for morbidity due to conditions such as BPD, an entity that was first described by Northway and associates in 1967 (201). BPD occurs almost exclusively in premature infants who received mechanical ventilation. Its incidence varies considerably from one report to another because of differences in patient susceptibility and management practices in different populations and institutions, as well as the definition employed. BPD has been defined as a requirement for supplemental oxygen at 28 days of age or at 36 weeks postmenstrual age, with characteristic radiographic findings (245). The clinical definition of BPD as a supplemental oxygen requirement at 28 days of age which was once widely used has been criticized, especially for extremely low birth weight in-

fants (birth weights of 500 to 750 g) because oxygen need at 28 days may simply reflect lung immaturity. Therefore, oxygen requirement and the presence of radiographic abnormalities at 36 weeks postmenstrual age may be a better predictor of adverse pulmonary outcome. Bancalari et al. (20) have provided an in-depth discussion of issues related to the definition of BPD and how this can affect incidence figures, as well as complicate interpretation of research studies.

Bancalari et al. (20) reported an incidence of BPD ranging from 67% among infants with birth weights of 500 to 750 g to less than 1% in infants weighing 1,250 to 2,500 g. Thus, BPD is now very uncommon in infants born after 32 weeks of gestation. Widespread use of antenatal steroids has reduced the occurrence of severe respiratory distress syndrome in more mature infants and at the same time has led to enhanced survival of more immature infants who are at higher risk for developing BPD (20). Administration of exogenous surfactant has decreased mortality but has not been shown to affect the incidence of BPD independently of other variables (20). The etiology of BPD is multifactorial and complex. Lung tissues of preterm infants lack sufficient surfactant and have incomplete alveolarization to provide an adequate ventilatory surface. The pulmonary immaturity of preterm neonates leads to diffuse microatelectasis and poor compliance. These factors make the immature lungs more susceptible to oxidant injury from supplemental oxygen delivery and volutrauma to the airways during mechanical ventilation. In recent years, an appreciation for the role of inflammation as a consequence of perinatal infection emerged as important in the pathogenesis of BPD, leading the way for consideration of perinatal pathogens such as *Ureaplasma* spp. as causal factors (182).

Proinflammatory cytokines are believed to play an important role in mediating pathology in a variety of lung diseases, including BPD, through innate and adaptive immune responses. These include interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), and IL-6. IL-1β and TNF-α activate the immune system, produce inflammation, and induce the release of IL-6, which affects the proliferation of antibody-producing B cells but also limits pulmonary inflammation associated with pneumonia and hyperoxia (187). In the mature immune system, activation of the inflammatory pathway is opposed by the production of cytokines such as IL-10 which down-regulate inflammation and host defense mechanisms in order to protect from an excessively strong response to stimuli. Small amounts of IL-10 in lung lavages of intubated preterm infants with respiratory distress suggests that the immature immune system has a limited ability to down-regulate the inflammatory response (187).

Higher levels of infection-induced amniotic fluid inflammatory cytokines may initiate lung injury in utero and have been associated with higher rates of BPD in preterm neonates delivered to women within 5 days after having amniocentesis to evaluate for infection (340). Moreover, tracheal aspirate inflammatory cytokine concentrations from infants with BPD are elevated in comparison to infants with self-limited respiratory distress syndrome (187). Elevated tracheal cytokines detected in neonates on the first postnatal day has also been associated with prolonged rupture of fetal membranes and histologic chorioamnionitis (187). Dyke et al. (80) found that the presence of *Ureaplasma* spp. in gastric aspirates of preterm neonates was associated with a significantly greater risk of developing BPD in those infants delivered by cesarean section but not in those who delivered vaginally, suggesting the possibility that longer exposure to inflammation in utero may be the explanation.

A large study of more than 1,600 very low birth weight infants (306) was designed to determine the contribution made by infection in utero versus infection and inflammation beginning after birth on neonatal outcome. These investigators compared rates of BPD in infants who were mechanically ventilated, in infants with histologic evidence of maternal chorioamnionitis, and in infants with postnatal sepsis. Chorioamnionitis alone reduced the risk of BPD, perhaps by inducing maternal corticosteroid production and hastening fetal lung development. However, in infants exposed to maternal chorioamnionitis and who required more than 7 days of ventilation, the risk for BPD was increased. These data suggest that there is a subset of infants who suffer greater damage from infection in utero, or that there is a subset of pathogens that may cause more severe and lasting damage to fetal lung tissue.

Postnatal sepsis and mechanical ventilation for more than 7 days independently increased the risk of BPD, indicating that continuing inflammatory stimuli from infectious or mechanical causes after birth play a role in the development of BPD. Data from studies such as those described above and summarized by Manimtin and coworkers (187) clearly implicate inflammation from perinatal infection with subsequent development of BPD. They further suggest that an imbalance in the neonatal cytokine milieu in response to inflammation could explain the excessive lung damage seen in infants with BPD, whether induced by mechanical ventilation, or by maternal or fetal infection.

Ureaplasma spp. are the most common microbes isolated from infected amniotic fluid, placentas, and the respiratory tracts of preterm infants and their ability to induce inflammation in these sites is undeniable (2, 44, 45, 47, 150, 339). Knowledge of the biology of ureaplasmas and their behavior in the respiratory tract of preterm neonates suggest that lung disease associated with these organisms is not necessarily due to direct damage from the bacteria themselves, but rather because of their potent stimulation of proinflammatory cytokines (TNF-α, IL-1β, and IL-8) or perhaps blockage of counterregulatory cytokines (IL-6 and 1L-10).

Several recent investigations have examined the relationship between ureaplasmal colonization of the neonatal respiratory tract and release of inflammatory mediators that may be involved in pathogenesis of BPD, including clinical studies (154, 214, 309) evaluation of cell lines from humans or rodents cultivated in vitro and exposed to *Ureaplasma* antigen (59, 166–169, 187), and animal models (308, 338). *Ureaplasma* spp. colonization of the respiratory tract in neonates has been consistently associated with increases in proinflammatory cytokines in tracheal secretions, including TNF-α, IL-1β, and IL-8 (68, 106, 214, 309). Blocking expression of IL-6 and/or IL-10 has also been reported in association with ureaplasmal colonization (187), although some reports have noted an increase in IL-6 in association with ureaplasmal colonization (154).

Li et al. (167) demonstrated that human and rodent macrophage cell lines exposed to *Ureaplasma* antigen will produce TNF-α and IL-6. This group subsequently provided additional in vitro evidence that *Ureaplasma* spp. may be involved in the

initiation of pathological changes in BPD by demonstrating that a human macrophage cell line exposed to *Ureaplasma* antigen releases vascular endothelial growth factor and intercellular adhesion molecule 1 (ICAM-1). Vascular endothelial growth factor is involved in pathological changes in the lung that occur in BPD through modulation of angiogenesis, whereas ICAM-1 mediates neutrophil activation and transendothelial migration of leukocytes to sites of inflammation (166). Moreover, the production as well as the expression of ICAM-1 and vascular endothelial growth factor mRNA were inhibited by steroids.

Manimtin et al. (187) have suggested that the alteration of the host inflammatory cytokine response mediated by *Ureaplasma* spp. occurs in conjunction with a coinflammatory stimulus such as concurrent bacterial infection or hyperoxia. To test this hypothesis, they measured cytokine release in peripheral blood monocytes that were unstimulated versus those stimulated with *Ureaplasma* antigen alone, and *Ureaplasma* antigen in combination with lipopolysaccharide (LPS). The interesting findings of this study were that *Ureaplasma* alone and in combination with LPS induced changes in cytokine release. In vitro inoculation with a low-inoculum partially blocked the LPS-stimulated IL-6 release by all cells and reduced LPS-stimulated IL-10 release by preterm cells; stimulated TNF-α and IL-8 release by preterm cells; and augmented LPS-stimulated TNF-α release in all cells. In preterm cells, high inoculum of *Ureaplasma* stimulated TNF-α and IL-8, but not IL-6 or IL-10, release; augmented LPS-stimulated TNF-α and IL-8 release; stimulated release of all four cytokines in term cells and IL-8 release in adult cells; and augmented LPS-induced TNF-α, IL-10, and IL-8 release in term cells but did not significantly affect LPS-induced cytokine release in adult cells. The authors concluded that the failure to stimulate IL-6 might impair organism specific lymphocyte responses, enhancing persistence of ureaplasmas in the lower respiratory tract and continued expression of the inflammatory cascade.

In addition to stimulating release of cytokines, ureaplasmas have been studied for their abilities to stimulate release of other inflammatory mediators. Nitric oxide is a soluble, short-acting free-radical gas produced by a variety of cells that mediates a number of functions involved in the local inflammatory response. Two studies have demonstrated the ability of *Ureaplasma* to stimulate rodent macrophage cell lines to release nitric oxide (59, 169). Nitric oxide production induced by *Ureaplasma* can be down-regulated by administration of corticosteroids (169).

Apoptosis of type II pneumocytes and pulmonary mesenchymal cells has been shown to occur as part of the pathogenesis of BPD in preterm infants (168). When lung epithelial cells undergo apoptosis, pulmonary fibrosis can occur as a consequence. Apoptosis of macrophages may also play a role in development of BPD since this would impact their ability to phagocytose neutrophils. Unchecked, the proliferation of neutrophils at the site of lung infection will lead to prolonged inflammation by means of cytokine production and release of proteases and oxygen free radicals (104). Using human macrophage and lung epithelial cell lines, Li et al. (168) have demonstrated that when these cells are stimulated with *Ureaplasma* antigen, apoptosis will occur in vitro as evidenced by morphological evaluation and analysis of DNA fragmentation.

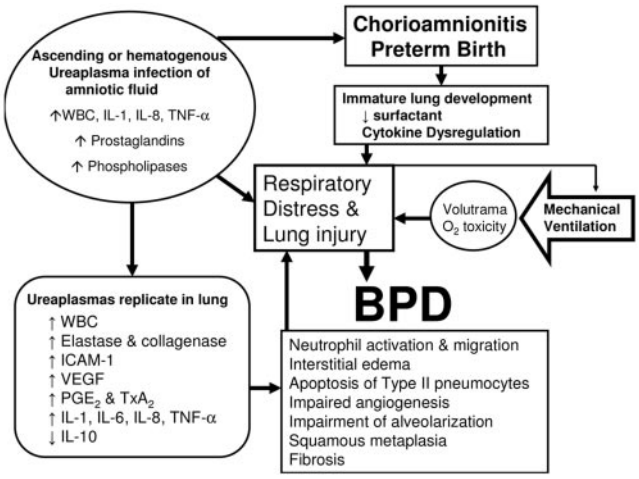

FIG. 2. Proposed scheme for involvement of *Ureaplasma* spp. in the pathogenesis of bronchopulmonary dysplasia.

They were also able to determine indirectly that the apoptosis of macrophages was driven by TNF-α production, since cell death was partially prevented when anti-TNF-α monoclonal antibodies were used to neutralize the cytokine production.

Cassell et al. (44) proposed that ureaplasmal infection contributes to the pathogenesis of BPD in very low birth weight neonates by causing pneumonia that initially goes undetected and untreated which leads to higher oxygen requirements in infected infants. These higher oxygen levels then create a vicious cycle of inflammation and damage due to increased ventilatory rates and pressures during mechanical ventilation. Hyperoxia likely contributes further to pathological effects in the lung through production of free radicals, oxidant damage to pneumocytes and permeability changes in alveolar walls (58). Figure 2 illustrates a proposed scheme of the complex processes involved with intrauterine or natal acquisition of *Ureaplasma* spp. may play a role in the pathogenesis of BPD.

The data presented thus far with respect to the ability of ureaplasmas to produce inflammatory mediators and the case reports of acute ureaplasmal pneumonia clearly show the capabilities that exist at the bacterial level to induce lung damage. Further support for this hypothesis involving ureaplasmas and hyperoxia as risk factors for development of BPD comes from the animal model described by Crouse et al. (58). In that study, newborn mice were inoculated intranasally with either *U. urealyticum* (serotype 10) or sterile broth and then housed in either 80% oxygen or room air. Significantly more mice in the *Ureaplasma* group housed in 80% oxygen than in the room air-exposed group were culture positive 14 days after inoculation. Severity of lung lesions and mortality were significantly higher in the group housed in 80% oxygen and inoculated with *U. urealyticum* than in all other groups. Overall, this study is significant in that it proved that hyperoxia leads to the persistence of *U. urealyticum* in the lungs of newborn mice, acutely potentiates the inflammatory response, and turns an otherwise self-limited pneumonia into a lethal disease.

The results of the inflammatory cascade shown to occur in the studies described above can be reflected in the characteristic radiographic appearance of BPD in preterm neonates.

Multiple studies have specifically examined the radiographic course of infants with ureaplasma colonization. Crouse and coworkers (60) evaluated chest radiographs of 44 preterm infants colonized in the lower respiratory tract by *Ureaplasma* spp. in comparison to those who were culture negative and found that pneumonia was twice as common in the *Ureaplasma*-positive group (30% versus 16%). Importantly, precocious dysplastic changes in the lungs within 2 weeks of birth were significantly more common in the *Ureaplasma*-positive group, independent of gestational age, race, and sex.

A second retrospective study of 25 preterm infants whose tracheal secretions were culturally positive for *Ureaplasma* spp. and who had received mechanical ventilation found that while *Ureaplasma*-positive had fewer signs of respiratory distress initially, they were more likely to deteriorate clinically and radiologically and often required mechanical ventilation to be resumed (295). Chest radiographs of *Ureaplasma*-positive infants showed evidence of emphysematous changes as early as 5 days with a pronounced difference by day 10, supporting the earlier findings of Crouse et al. (60). A third study from Italy (209) corroborated the concept that infants from whom ureaplasmas are recovered in the lower respiratory tract develop precocious dysplastic radiographic changes. They found 9 of 40 (22.5%) ureaplasma-positive infants versus 1 of 42 (2.3%) ureaplasma-negative infants developed this condition ($P = 0.006$). In contrast, Cordero and coworkers (56) retrospectively evaluated the radiologic findings for 183 preterm infants with BPD and determined that ureaplasma colonization of the airways was not associated with particular radiographic changes or more severe BPD compared with infants with gram-positive cocci or gram-negative bacilli in their airways.

Since the initial reports in 1988 of an association of ureaplasmal colonization of the lower respiratory tract and development of BPD in preterm infants, there have been a large number of published studies from countries around the world. The best available evidence in humans comes from cohort analyses of infants at risk for development of BPD, either with or without *Ureaplasma* colonization. Some of the subsequent studies concurred with the original observations; however, others cast doubt on the association of *Ureaplasma* spp. and development of BPD. Interpretation of some of the 30-plus studies published to date has been hampered by small numbers of patients, which raises the possibility that statistical significance may not have been achieved because of inadequate power. In addition, the proportion of the eligible population sampled is not always stated. Extent of use of mechanical ventilation, artificial surfactant, and steroids may also influence results of investigations as do the characteristics of the study populations, gestational ages, birth weights, and timing and number of specimens examined for the presence of ureaplasmas. Since ureaplasmas are fastidious microorganisms, the method of detection, adequacy of microbiological media to support their growth, and use of PCR assays can lead to differences in outcomes. Finally, the definition of BPD is not uniform in all studies.

We have reviewed a total of 36 articles in peer-reviewed journals originating from around the world that identified a cohort of neonates screened for the presence of *Ureaplasma* by culture with or without PCR and followed prospectively for the development of BPD (252). Population completeness was considered acceptable if the majority of patients meeting predetermined study criteria were enrolled. Studies were excluded if the proportion of eligible patients enrolled was not described or if patients were enrolled on the basis of specimen results without an explicit protocol. The studies were also grouped by definition of BPD, oxygen requirement at 28 days postnatal age (BPD28) and/or 36 weeks postmenstrual age (BPD36). Twenty-three articles reported *Ureaplasma* colonization and BPD28 (2, 6, 7, 13, 45, 49, 62, 89, 109, 111, 123, 128, 134, 137, 208, 209, 215, 216, 241, 247, 250, 307, 329) and eight reported BPD36 (49, 89, 109, 111, 127, 208, 209, 216). There were 2216 infants included in the BPD28 group and 751 infants in the BPD36 group.

Table 3 summarizes the prospective studies investigating the role of *Ureaplasma* spp. in the pathogenesis of BPD meeting these criteria. In our analysis (252), pooled BPD28 studies showed a significant association between *Ureaplasma* colonization and development of BPD ($P < 0.001$). Combined analysis of BPD36 studies also showed a significant association between *Ureaplasma* colonization and development of BPD ($P < 0.009$). This analysis complements the earlier meta-analysis by Wang et al. published in 1995 (330) which showed a significant association between the presence of *Ureaplasma* spp. in the lower respiratory tract and colonization and subsequent development of BPD28 in most investigations, but there were insufficient data available at that time to evaluate *Ureaplasma* colonization and BPD36, which is now the preferred diagnostic criterion for this condition.

Given the limitations of these data, the routine culture for *Ureaplasma* and treatment of colonization with the aim of preventing BPD should still reside in the arena of clinical investigation. These data also indicate that techniques beyond culture (i.e., PCR) should be evaluated and if accurate, brought into the clinical arena. In order to fully evaluate whether a causal relationship exists between colonization of preterm neonates by *Ureaplasma* and development of BPD, a large multicenter therapeutic trial will be needed. A randomized placebo-controlled treatment trial may not prove a causal association between *Ureaplasma* spp. and BPD. However, if treatment with a suitable agent appropriate for use in neonates such as a macrolide antibiotic demonstrates a benefit such as a measurable decrease in rates of BPD and its associated morbidity, this could have a major impact on the management of preterm neonates. Further discussion of treatment of neonates with respiratory disease associated with *Ureaplasma* spp. is provided in a subsequent section.

SYSTEMIC INFECTIONS IN THE NEONATE

Bacteremia

The factor associated most significantly with sepsis due to any microorganism in the neonate is low birth weight (263). Other factors include prolonged ruptured membranes, traumatic delivery, maternal infection, chorioamnionitis, and fetal hypoxia.

In the case of genital mycoplasmas, infection can occur at the time of birth or in utero. *Ureaplasma* spp. and *M. hominis* have been isolated from cord blood and there have been numerous reports of their isolation from the bloodstream of neonates and young infants, sometimes in association with

TABLE 3. Summary of selected studies evaluating the association of *Ureaplasma* spp. and bronchopulmonary dysplasia

Reference	Year	Specimen[a]	No. of specimens/no. tested (%)[b]					
			BPD28			BPD36		
			BPD/US positive	BPD/US negative	*P*	BPD/US positive	BPD/US negative	*P*
Abele-Horn (2)	1998	ETA	22/35 (63)	22/40 (55)	≤0.05			
Acosta (6)	1999	ETA/throat	9/27 (33)	21/74 (28)	NS			
Agarwal (7)	2000	ETA	8/9 (89)	12/28 (43)	0.01			
Alfa (13)	1995	ETA/throat/surface	5/5 (100)	7/21 (33)	0.028			
Cassell (45)	1988	ETA	9/24 (38)	21/101 (21)	<0.02			
Castro-Alcaraz (49)	2002	ETA/NP/Throat	14/40 (35)	15/80 (19)	<0.001	7/40 (18)	1/78 (1)	<0.001
Da Silva (62)	1997	ETA/NP	26/40 (65)	39/68 (57)	NS			
Galetto Lacour (89)	2001	ETA/NP	7/7 (100)	10/38 (26)	<0.001	2/7 (29)	3/38 (8)	0.11
Hannaford (109)	1999	ETA	22/34 (65)	38/78 (49)	NS	15/34 (44)	23/78 (30)	0.03
Heggie (111)	2001	ETA				35/66 (80)	60/109 (58)	NS
Horowitz (123)	1992	ETA/NP	4/10 (40)	4/41 (10)	<0.04			
Iles (127)	1996	ETA				13/15 (87)	11/25 (44)	0.02
Izraeli (128)	1991	ETA/throat	3/4 (75)	5/16 (31)	NS			
Jonsson (134)	1994	ETA, NP	10/17 (59)	21/72 (29)	0.02			
Kafetzis (137)	2004	ETA/NP	8/30 (27))	9/96 (9)	0.03			
Ollikainen (208)	2001	ETA/blood	22/39 (56)	40/85 (47)	NS	17/39 (44)	33/85 (39)	NS
Pacifico (209)	1997	ETA/NP/blood	20/47 (69)	9/47 (53)	0.01	11/12 (92)	5/20 (25)	0.0006
Payne (215)	1993	ETA/NP	10/12 (83)	37–74 (50)	0.024			
Perzigian (216)	1998	ETA	15/22 (68)	30/83 (36)	<0.02	6/22 (27)	18/83 (220)	NS
Ruf (241)	2002	Throat	5/17 (29)	0/57 (0)	0.05			
Sanchez (247)	1988	Surface/throat	14/46 (30)	5/65 (8)	<0.05			
Saxén (250)	1993	ETA	6/14 (43)	10/35 (29)	NS			
Van Waarde (307)	1997	ETA	52/108 (48)	9/97 (9)	NS			
Wang (329)	1988	ETA/NP/GA	23/43 (53)	9/52 (17)	<0.005			

[a] ETA, endotracheal aspirate; NP, nasopharynx; GA, gastric aspirate; US, *Ureaplasma* species; NS, not significant.
[b] BPD28, supplemental oxygen requirement at 28 days of postnatal life; BPD36, supplemental oxygen requirement at 36 weeks postmenstrual age.

pneumonia and/or meningitis (33, 38, 45, 64, 207, 209, 302, 318, 323, 333). Waites et al. (323) performed blood cultures for mycoplasmas in 43 newborn infants as part of a study of cerebrospinal fluid infections. Two infants were positive for *M. hominis* and two were positive for *Ureaplasma* spp. Cassell et al. (45) found that 26% of preterm infants with positive endotracheal aspirates had positive ureaplasmal blood cultures.

Ureaplasmal bacteremia may accompany severe neonatal pneumonia (38, 318). Two investigators have isolated *Ureaplasma* spp. from the bloodstream of neonates in association with fatal pneumonia and persistent pulmonary hypertension of the newborn (38, 318), conditions with clinical manifestations that were very similar to what is encountered with another well-known neonatal pathogen, group B streptococcus. Dan et al. (64) reported a case of *M. hominis* septicemia documented on two separate occasions 11 days apart in a 10-month-old infant who had suffered extensive burns. An antibody response to the mycoplasma was also detected. In contrast to the above findings, other studies in neonates (80, 128) and in older infants up to 3 months of age readmitted to the hospital for suspected sepsis (171) were unable to detect genital mycoplasmas in bloodstream infections. It appears unlikely that genital mycoplasmas are a significant cause of bloodstream infection outside of the neonatal period in otherwise healthy infants. However, under special circumstances their presence should be considered.

Infections of the Central Nervous System

The incidence of bacterial meningitis is greater in the neonatal period than in any other period in life, yet even in this select group epidemiological surveys place the attack rate at less than 1% (44). However, these figures do not include infections caused by mycoplasmas and ureaplasmas.

The first reports of meningitis due to an organism that was most likely *M. hominis* were published in the 1950s and since that time there have been numerous case reports, and multiple prospective studies that have identified cases of meningitis caused by this mycoplasma in both preterm and full-term neonates, some of whom had neural tube defects, though others were neurologically intact (14, 31, 120, 188, 194, 256, 305, 319, 320, 323, 333). Although not as common as reports of *M. hominis* isolations from cerebrospinal fluid (CSF), there have been several case reports and prospective studies published since the1980s proving that *Ureaplasma* spp. are also causes of meningitis in preterm and full-term neonates (91, 115, 199, 207, 256, 257, 268, 305, 320, 323). In addition to meningitis, both genital mycoplasmas have been detected in a brain abscess in a neonate (228) and ureaplasmas have been isolated directly from brain tissue of preterm twins who died soon after birth (206). The fact that there have been more cases of *M. hominis* meningitis described than cases involving *Ureaplasma* spp. is most likely due to the fact that many cases of *M. hominis* meningitis were discovered accidentally since this mycoplasma will often grow on routine bacteriological media whereas ureaplasmas require special media and growth conditions for their detection.

Mycoplasmal infections of the central nervous system in neonates were reviewed in this journal in 1993 (47) and considerable detail was provided describing the individual reports and case series published up until that time. Since then, additional prospective studies of neonates with suspected infections

have shown that these organisms can be detected in CSF in ill neonates. Sethi (256) performed cultures for genital mycoplasmas on 66 CSF samples and 49 tracheal aspirates taken from 100 low birth weight infants who had suspected meningitis and/or respiratory distress, respectively. *Ureaplasma* spp. was isolated from 9% of CSF samples and 14% of tracheal aspirates. *M. hominis* was isolated from the CSF in one case but from none of the tracheal aspirates. Three out of seven mycoplasma-infected central nervous system cases showed CSF pleocytosis.

There appears to be an association between CSF infections with ureaplasmas and the development hydrocephalus and intraventricular hemorrhage in preterm infants that bears further study (206, 323). Valencia (305) studied 69 neonates who underwent a diagnostic workup for suspected sepsis and found that 9 had positive CSF cultures for *M. hominis* and 1 infant had a positive CSF culture for *Ureaplasma* spp. All blood cultures were sterile. Only one of the infants with a positive CSF culture for *M. hominis* had clinical evidence of systemic infection. These reports confirm studies by Waites et al. (319, 320, 323) that genital mycoplasmas can be detected as common causes of meningitis in neonates when appropriate procedures are used for their detection and that not all cases in which these organisms are detected in CSF by culture will result in clinical disease. These earlier reports that some cases of mycoplasmal or ureaplasmal meningitis will resolve spontaneously, even in the presence of an inflammatory reaction in the CSF, have been corroborated by more recent reports (199).

Since some cases can be associated with prolonged and repeated isolations from CSF, such infections cannot be dismissed as inconsequential and require careful follow-up. In our initial reports of meningitis due to genital mycoplasmas (319, 320, 323), four ureaplasma-infected infants died and one case of *M. hominis*-induced central nervous system infection occurred in a full-term infant in whom the clinical features of congenital infection resembled those seen with viral or toxoplasmal infections and in whom major neurological impairment was noted. Some cases occurred in association with isolation of the same organisms from the bloodstream and/or lower respiratory tract and in infants with severe intraventricular hemorrhage.

As might be expected, not all investigations have detected genital mycoplasmal infections in infants with meningitis, even when appropriate methods were employed (171, 188). However, the study by Likitnukul involved primarily older term infants, all of whom had been previously discharged from the hospital and had returned because of suspected sepsis or meningitis (171), as opposed to the younger mainly preterm infants that seem most susceptible to systemic infections due to these organisms. Shaw et al. (257) performed a prospective study of 135 preterm infants undergoing lumbar puncture and found only one isolate of *Ureaplasma* spp. These investigators felt the single isolate did not justify routine investigation of infants for mycoplasmal infection. However, a similar or even lower isolation rate of other bacteria from CSF does not justify withholding diagnostic procedures to identify bacterial infections. Not enough is known about the long-term effects of perinatal mycoplasmal infections to ignore their presence. Cassell (44) suggested that spread of these organisms to the central nervous system occurs directly through the respiratory tract in many cases rather than the bloodstream, since several reports involve infants with negative blood cultures and positive respiratory cultures.

Based on the limited number of cases reported in the literature to date, it is impossible to speculate about the typical course of mycoplasmal or ureaplasmal infections of CSF. We suggest that the severely ill infant with meningitis may in fact represent only a fraction of the total number of infants infected by these organisms and many others may have only a mild, often subclinical infection that resolves spontaneously. Long-term neurodevelopmental outcomes of infants with central nervous system infections caused by the genital mycoplasmas are poorly understood for multiple reasons. Cases in which there was follow-up beyond the neonatal period were mainly preterm neonates whose subsequent course was complicated by other conditions associated with prematurity that could not readily be separated from infection.

Other Infections

The respiratory tract, bloodstream, and central nervous system are the body sites for which the greatest amount of information is available with respect to infections that occur in neonates and young infants. However, there are some case reports of other types of infections that have appeared in the literature from time to time. One of the very earliest reports of genital mycoplasmas in neonatal infection was a report from 1968 in which *M. hominis* was isolated from purulent drainage of 8 of 250 infants with conjunctivitis (133). The significance of this study is uncertain because this mycoplasma may sometimes be isolated from noninflamed conjunctivae.

M. hominis has been isolated from pericardial fluid in an infant born with respiratory distress related to cardiac tamponade (92). In this case, the infant recovered after placement of a pleuropericardial window and a course of intravenous antimicrobials. This mycoplasma has also been shown to cause abscesses in infants, sometimes as a result of forceps delivery or intrapartum fetal monitoring, and has been isolated from purulent drainage from a lymph node in an infant with submandibular adenitis (95, 220, 244). Abscesses associated with fetal monitors have also been shown to be due to *Ureaplasma* spp (108). A case of fatal nonimmune hydrops fetalis was reported in which *Ureaplasma* spp. was isolated in bronchial secretions, lung tissue and brain tissue, suggesting these organisms should be considered in the differential diagnosis of hydrops fetalis which may in some instances be caused by infections (205).

Since the normal habitat of genital mycoplasmas in adults is the urogenital tract, it is logical that this might also be a source of colonization and disease in neonates, but few studies have investigated the possibility. Likitnukul et al. (171) cultured 170 specimens of urine obtained from infants up to 3 months of age who were rehospitalized because of suspected infection. They identified *M. hominis* in six patients, *Ureaplasma* spp. in nine, and both organisms in one patient. Twelve of the positive cultures were voided urine specimens, and four were suprapubic bladder aspiration specimens. The clinical significance of these findings is uncertain since the infants improved without specific therapy for genital mycoplasmas.

DIFFERENTIAL PATHOGENICITY OF *UREAPLASMA UREALYTICUM* AND *UREAPLASMA PARVUM*

Soon after ureaplasmas were first identified and characterized it became apparent that these organisms could be subclassified into several distinct serotypes. The number of serotypes was eventually expanded to 14 (235). Additional study over several years, using data obtained from 16S rRNA sequencing, led to the further breakdown of the 14 serotypes into two biovars or clusters. Biovar 1, also known as the parvo biovar, contains serotypes 1, 3, 6, and 14, while biovar 2, also known as the T960 biovar, contains serotypes 2, 4, 5, 7, 8, 9, 10, 11, 12, and 13. Recently, the two biovars, whose DNA homology is less than 60%, were designated as distinct species. Biovar 1 became *U. parvum* and biovar 2 became *U. urealyticum* (110, 152, 153, 234, 236, 238). Biovar 1 (*U. parvum*) is the more common of the two biovars isolated from clinical specimens, but both species may occur simultaneously in some people.

Prior to division of the two biovars into separate species, numerous studies utilizing a direct approach to typing the organisms grown from culture by a variety of techniques such as polyclonal or monoclonal antibodies (81), immunofluorescence (198), immunoperoxidase (222), agar growth inhibition (259), and an indirect approach using serology to measure antibody responses to specific serotypes in targeted patient populations (226, 227) attempted to ascertain differential pathogenicity of ureaplasmas at the serotype level. Results were varied and inconsistent due to a great extent to the inefficient and imprecise methods available for serotype differentiation at the time, occurrence of multiple cross-reactions, and the fact that many persons may harbor more than one serotype in their urogenital tract in the presence or absence of disease. Development of monoclonal antibodies enabled identification of multiple-banded antigens responsible for serotype specificity on the cell surface (347).

Several studies showed no consistent predominance of any *Ureaplasma* serotype in men with nongonococcal urethritis (NGU) or differences from serotypes detected in asymptomatic controls while others have found serotype 4 to occur more commonly in this condition (57, 218, 259, 270). Lin (173) found no differences in the serotype distribution in normal college women, women with salpingitis, and pregnant women who delivered normal, low-birth-weight, or stillborn infants. Naessens et al. (198) typed 240 ureaplasma strains isolated from cervices, placentas, or fetal tissues in women with a history of recurrent abortion, women who had had their first spontaneous abortion, pregnant women with premature delivery or intrauterine death), and women with uneventful pregnancies. Serotype 6 was the predominant type detected in urine samples according to one study (116). Serotype 4 was significantly more common in the cervices of women with recurrent abortions (20.8%) than in those of control patients (5.1%).

Quinn et al. (227) compared antibody titers for ureaplasma serotypes 1 to 8 at delivery in 14 women with histories of pregnancy wastage and in their infants with titers in 20 normal mother-infant pairs. Infants of mothers with pregnancy losses exhibited significantly elevated mean titers to serotypes 6 and 8, while the mothers had elevated mean titers to serotypes 4 and 8. A lack of significantly elevated antibody titers to serotype 3 has been used by these investigators to suggest that serotypes 4 and 8 may be more pathogenic. They have also suggested that the fact that serotype 8 produces more phospholipase A2 than serotypes 3 and 4 may explain involvement of this serotype in premature birth. However, in the study by Naessens (198), there were no isolations of serotype 8 from cervices or placentas of women who experienced intrauterine fetal death or premature delivery.

Quinn (226) evaluated the serologic responses (but not culture status) of preterm infants with respiratory distress and compared them with the responses and status of normal term infants. Neonates with respiratory disease had significantly elevated mean titers to serotypes 4, 7, and 8 compared with mean titers of normal neonates and slight but not significant elevations of titers to serotypes 3 and 6. When the respiratory disease cases were assessed according to whether the infant survived or died, the mean titer to serotype 3 was slightly elevated in all groups. With serotypes 4 and 8, the mean titers were significantly higher among neonates who died than among the survivors. For serotype 5, a significant elevation occurred only among the survivors. The difficulty in interpreting these results is that sera were collected from infants with respiratory disease from 0 to 20 days after birth and from the control term infants at delivery only. Also, the frequent transfusions received by premature infants may affect immunoglobulin levels. Investigations in which ureaplasma isolates were identified directly on the primary isolation plates from larger numbers of patients have not confirmed results of the other studies linking serotype 4 to urethritis and spontaneous abortion (233, 270).

Zheng (348) evaluated 10 ureaplasmal isolates from neonatal cerebrospinal fluid and three bloodstream isolates using serotype-specific reagents and monoclonal antibodies. Seventy percent of the CSF isolates represented 5 of the 14 established serotypes and both genomic clusters, now designated *U. parvum* and *U. urealyticum*. These data support the hypothesis that the property of invasiveness for ureaplasmas is likely not limited to one or a few particular serotypes. Additionally, this study showed that, even in isolates of the same serotype from different patients and in isolates from different body sites within the same patient, there can be size variation in the serotype antigens expressed. Therefore, it appears that many serotypes are invasive and that perhaps antigen variability and host factors may be more important determinants for ureaplasma infections than different serotypes.

Availability of more powerful typing techniques through the PCR assay and a shift in focus from the serotype level to the biovar or species level has led to more information concerning differential pathogenicity among ureaplasmal strains in more recent studies. Several studies have described various schemes based on the PCR assay for organism detection and determination of biovars and serotypes of *Ureaplasma* spp. (151, 153, 219, 238, 294). Some of these methods have been applied directly to address the question of differential pathogenicity.

There was no difference in pregnancy outcome and magnitude of intra-amniotic inflammatory response, chorioamnionitis, birth weight or gestational age at delivery or neonatal morbidity in 77 women whose amniotic contained ureaplasmas detected by PCR attributable to biovar (146). Deguchi and coworkers recently reexamined the presence of *U. parvum* and

U. urealyticum in NGU and found a significantly higher prevalence of *U. urealyticum* compared to *U. parvum* for which prevalence was not significantly different from men without NGU (74). The T960 biovar (*U. urealyticum*) has been found to be dominant in patients with pelvic inflammatory disease as well as in patients who had had a miscarriage, and it seemed to have more adverse effects on pregnancy outcome, as assessed by birth weight, gestational age, and preterm delivery, than the parvo biovar (*U. parvum*) according to a study performed in Germany (4).

Heggie et al. (111) were unable to attribute a greater risk of developing BPD among 66 *Ureaplasma*-colonized infants and also found no differences between infants harboring *U. parvum* compared to those with *U. urealyticum*. However, Abele-Horn (4), reported that 10 of 18 (56%) of infants colonized by *U. urealyticum* developed BPD versus 12 of 48 (25%) infants with *U. parvum* ($P < 0.05$). Katz et al. (139) compared the occurrence of *U. urealyticum* and *U. parvum* in 181 infants with birth weights of <1,500 g whose endotracheal aspirates were culture positive for *Ureaplasma* spp. over a 10-year period and found no significant difference or trend in prevalence of either species in infants with or without BPD, but there was a significantly greater likelihood of BPD among infants whose endotracheal aspirates were positive for both *Ureaplasma* spp. (OR = 3.02; 95% CI 1.19 to 7.69, $P = 0.012$). Limitations of this study include its retrospective nature with no criteria for obtaining endotracheal aspirates, leaving many infants who were never tested for ureaplasmas, the fact that only culture-positive specimens were tested by PCR for determining the species of the organisms, and only one endotracheal aspirate was tested per patient. It is possible that other ureaplasma-positive infants might have been detected had additional samples been tested.

When PCR was used to compare the distribution of species and prevalence of *tetM* in 63 isolates of *Ureaplasma* spp. obtained from amniotic fluids of women with adverse pregnancy outcomes and 22 isolates from the lower urogenital tract of healthy pregnant women, no differences were seen in tetracycline susceptibility or the occurrence of the two species between the two groups (189). Our recent unpublished findings that included evaluation of 45 *tetM*-positive ureaplasmas also found no significant difference in its occurrence in *U. parvum* versus *U. urealyticum.* In contrast, two other studies found more tetracycline resistance in the T960 biovar (*U. urealyticum*) than the parvo biovar (*U. parvum*) (78). Based on these limited observations, whether the two *Ureaplasma* species are likely to have differential susceptibility to tetracycline based on the presence or absence of *tetM* is unresolved. Such differences, when they are observed, may be more likely to reflect the history of antimicrobial exposure and other local environmental and host factors than a different capacity of the organism to acquire *tetM*. Additional studies must be performed to determine the extent to which any differential pathogenicity of *Ureaplasma* species actually occurs and under what circumstances. The availability of real-time PCR assays for differential detection and quantification of *U. urealyticum* and *U. parvum* may prove to be very useful in determining their respective roles in disease (184).

HOST DEFENSES IN THE NEONATE

Very low birth weight infants are especially susceptible to bacterial and fungal infections (272). These infants have relative deficiencies in mucosal barrier function and in both the innate and adaptive immune responses. The immature host may generate limited type-specific antibody production in response to invading pathogens and the amount of secretory IgA may also be lower in mucosal surfaces than in more mature neonates (140). Deficiencies in serum complement components, defensins, fibronectin, and abnormalities in cytokine production contribute further to the relative immunodeficiency of the premature infant (253). Cellular deficiencies of chemotaxis, phagocytosis, and microbial killing add to the vulnerability of preterm neonates to systemic infections, including bloodstream invasion (140). These deficiencies explain, in part, the systemic spread of bacteria, including the genital mycoplasmas, after colonization of the respiratory tract mucosa.

Clinically significant ureaplasmal infections rarely occur in infants born after 34 weeks of gestation. The virtual absence of ureaplasmal disease in the more mature host suggests the importance of antibody in host defense against these organisms. Very low birth weight infants receive far less maternally derived immunoglobulin from placental transfer which normally occurs in the later stages of gestation.

Additional support for the concept that host antibody is critical in defense against systemic ureaplasmal infections comes from numerous case reports and studies in older children and adults with hypogammaglobulinemia. *Ureaplasma* spp. are the most common bacteria isolated from infected joints in persons with this condition. Repeated and prolonged episodes of arthritis over several years, sometimes associated with antibiotic-resistance, that responded only to the administration of specific hyperimmune serum have been described (288). Apart from joint involvement, subcutaneous abscesses, persistent urethritis, and urethrocystitis/cystitis in hypogammaglobulinemic patients have also been associated with ureaplasmal infection (288).

Data reported by Quinn et al. (225–227) also suggest that selective antibody to certain serotypes increases in women with pregnancy wastage and in infants with respiratory disease compared with control patients. Work by Gallo et al. (90) suggests that the presence of *U. urealyticum*-specific IgM antibody in infants is predictive of disease.

Taken together, the available evidence suggests but does not prove that immunity to invasive infection by *Ureaplasma* spp. is type specific. The mechanism of protection afforded by antibody seems to be mediated by metabolic inhibition of the organism rather than opsonization (288, 334).

OTHER MYCOPLASMAS FOUND IN THE UROGENITAL TRACT OF ADULTS

Due to their fastidious growth requirements and presumably less frequent occurrence than *Ureaplasma* spp. or *M. hominis*, much less is known about the epidemiology and disease associations of organisms such as *M. fermentans*, *Mycoplasma genitalium*, and *M. penetrans* in humans. Most of the studies evaluating *M. hominis* and *Ureaplasma* spp. did not use appropriate methods for the detection of the latter organisms. Utilization

of a molecular-based nucleic acid amplification method is critical since they are rarely isolated by culture. These mycoplasmas are now known to occur in the human urogenital tract of adults and have received considerable attention in recent years in studies focusing on a variety of pathological conditions. *M. pneumoniae* is also worthy of consideration as a cause of respiratory infections in persons of all age groups, though very few attempts have been made to determine whether it occurs in neonates and young infants. There have been no credible data implicating *M. spermatophilum* and *M. primatum* in human disease, and they need not be discussed further.

Mycoplasma fermentans

Attention was focused on *M. fermentans* in the late 1980s because of reports that it may be important as a mediator or cofactor in the development of AIDS (175, 177, 246). Taken in aggregate, the preponderance of evidence in subsequent studies utilizing improved detection methods, including the PCR assay, suggests that this mycoplasma is not important in the development of AIDS in the large majority of patients. However, it apparently can play a role as an opportunistic pathogen in this setting and occasionally in persons who are human immunodeficiency virus negative (28, 178, 284). The notoriety associated with the possibility that this mycoplasma may be involved in the pathogenesis of AIDS led to studies aimed at understanding how it may invade cells and produce disease in the human host.

Unlike *M. pneumoniae*, *M. fermentans* lacks a well-defined terminal attachment tip to mediate attachment and cell invasion. Recent work by Yavlovich et al. (337) demonstrated that *M. fermentans* binds plasminogen and converts it to plasmin, whereupon mycoplasmal cell surface proteins are altered to promote its internalization. The role of plasminogen activation as a virulence factor and other aspects of *M. fermentans* pathogenesis, including the importance of membrane surface proteins that mediate cell fusion, cytadherence, and antigenic variation, are discussed at greater length by Rottem (239).

M. fermentans can be detected in the upper and lower urogenital and respiratory tracts and bone marrow, and has been associated with a variety of systemic conditions in adults including inflammatory arthritis and pneumonia (8, 10, 12, 94, 178, 251, 281, 299, 311). *M. fermentans* has not been shown to have a pathogenic role in male urethritis (72, 287, 297). It has been recovered from the throats of 16% of children with community-acquired pneumonia, some of whom had no other etiologic agent identified, but the frequency of its occurrence in healthy children is not known (281). *M. fermentans* has also been detected in adults with an acute influenza-like illness who developed respiratory distress syndrome (178) and from bronchoalveolar lavage in AIDS patients with pneumonia, sometimes as the sole microbe, so it clearly has the potential to cause respiratory tract disease in susceptible hosts (9). This mycoplasma is also known to colonize mucosal surfaces in healthy persons, complicating efforts to understand its role in disease (11).

M. fermentans was not detected by culture or PCR in patients with urethritis or cervicitis but was detected by PCR in 4 of 232 amniotic fluid samples tested according to one study (29). These results suggest that *M. fermentans* can be transferred transplacentally. Histological evidence of villitis and chorioamnionitis was present in two of the four patients, suggesting that *M. fermentans* may be a cause of chorioamnionitis (29). This mycoplasma has also been detected in the placental chorionic villi, proving its ability to invade the upper reproductive tract (44). Inability to detect *M. fermentans* by culture or PCR assay in urine or cervical secretions in 94 men and 87 women who had urethritis or cervicitis further supports the fact that this mycoplasma is not an important cause of these conditions (44). We are unaware of any prospective studies in neonates to determine whether *M. fermentans* may be important as an agent of disease in this population. Waites and Talkington (311) recently reviewed the importance of *M. fermentans* in human diseases and provided more detail on the conditions described above as well as others.

Mycoplasma genitalium

M. genitalium was first isolated in 1981 from urethral specimens of men with urethritis (300). This mycoplasma has numerous similarities with *M. pneumoniae*, particularly the flask-shaped attachment organelle, terminal tip-like structure, as well as antigenic structures, and the ability to invade epithelial cells (129, 281). Understanding its role in human disease was greatly hampered by its slow growth, fastidious cultivation requirements, and serologic cross-reactivity with *M. pneumoniae* (129, 130, 174). A few subsequent reports of isolations of this mycoplasma in culture have been forthcoming, including some isolations from women (21, 22, 129, 181), but it was not until the availability of the PCR assay that investigation into the disease associations of this mycoplasma became fruitful.

Recent evidence from studies utilizing the PCR assay, complemented by investigations that employed serology, and experimental studies in primates, indicates that *M. genitalium* is of etiologic significance in approximately 25% of cases of nongonococcal urethritis and possibly prostatitis in men (73, 129, 160, 283), as well as cervicitis and pelvic inflammatory disease in women (15, 54, 185, 301). Serological evidence suggests indirectly that *M. genitalium* may play a role in some cases of tubal factor infertility, but this has not been confirmed by detecting the organism or its DNA directly in fallopian tubes of infertile women (53). *M. genitalium*, like the other genital mycoplasmas, may also be present in the lower urogenital tract in some healthy men and women.

Jensen et al. (130) summarized the results of 19 clinical studies investigating the role of *M. genitalium* in 2,069 men with nongonococcal urethritis and 1,810 men without nongonococcal urethritis and determined that this mycoplasma was present in 21.1% of those with nongonococcal urethritis versus only 6.7% of those without nongonococcal urethritis. Several studies have also assessed the prevalence of *M. genitalium* in the lower urogenital tract of women by the PCR assay. A prevalence ranging from 0 to 20% has been reported, but since women in whom this mycoplasma was detected were seeking health care in a sexually transmitted disease clinic, it is not clear from most of these reports how many of them had manifestations of infection that could have been related to its presence (67, 129, 131, 141, 210, 281, 289). Thus, these figures may not truly reflect the prevalence of *M. genitalium* in healthy

sexually active women. Thus far, there has been no association of *M. genitalium* with BV (129, 141, 185, 210).

Blanchard and coworkers used cultures and the PCR assay to determine whether *M. genitalium* was present in the urethra and cervix of sexually active adults and in the amniotic fluid of women whose membranes were intact and collected at the time of cesarean delivery (29). *M. genitalium* was detected by PCR but not by culture in 11% of patients with urethritis or cervicitis. It was not detected by either the PCR assay or culture in the 232 amniotic fluid samples analyzed or by culture from the chorioamnion of 609 women. Its occurrence in extragenital sites, including the upper (22) and lower respiratory tracts (67) of adults, proven by the PCR assay, suggested it might colonize the respiratory tracts of neonates as well.

A prospective study comparing culture and PCR to detect *Ureaplasma* spp., *M. hominis*, and *M. genitalium* in vaginal specimens of 47 high-risk pregnant women and from skin, throat, and endotracheal aspirates from eight neonates delivered to them found that *Ureaplasma* spp. were the most common organisms detected with 31 of 47 (61.7%) women colonized in the vagina, in comparison to 7 of 47 (15%) for *M. hominis*, and 1 of 47 (2%) for *M. genitalium* (180). These findings support the concept that *M. genitalium* is much less common than either *M. hominis* or *Ureaplasma* spp. in the lower urogenital tract of women. There were two infants born to colonized mothers who became colonized with *Ureaplasma* spp. A mother whose vaginal specimen was positive by the PCR assay for *M. genitalium* delivered a 1,125-g male infant who developed acute respiratory distress and from whom *M. genitalium* was detected by PCR assay performed on tracheal secretions soon after birth, suggesting that vertical transmission occurred. Consistent with earlier experience, attempts to detect *M. genitalium* by culture in this study were unsuccessful, requiring the PCR assay to determine its presence.

Labbe et al. (164) detected *M. genitalium* by the PCR assay in 6.2% of cervical specimens of 1,014 pregnant women in Guinea-Bissau. They were unable to relate the presence of *M. genitalium* in the cervix with stillbirth, spontaneous abortion, premature delivery, or small-for-gestational-age babies and concluded that this mycoplasma appears not to have any deleterious impact on outcome of pregnancy. Two other studies found *M. genitalium* in the cervical or vaginal secretions of very few pregnant women (less than 5%) using the PCR assay and were unable to relate its presence to premature birth (155, 179). However, as documented earlier in this review, many studies attempting to relate the presence of *M. hominis* and *Ureaplasma* spp. to adverse pregnancy outcome, neonatal infection, or diseases of the upper urogenital tract that limited their samples to the lower urogenital tract were unsuccessful, whereas studies examining their presence directly in the upper tract were sometimes able to show a relationship (43, 46, 82, 118, 162, 223, 224). Further investigations of *M. genitalium* as an agent of disease in pregnant women and neonates are warranted.

Mycoplasma penetrans

The attention focused on *M. fermentans* and its possible role in human immunodeficiency virus infection and AIDS led to the discovery of an additional mycoplasmal species from in humans and reevaluation of the possible significance of another. *M. penetrans* was first described in 1991, when it was detected in the urine of homosexual men infected with human immunodeficiency virus, but not from healthy age-matched volunteers (176). It was later reported to be associated with Kaposi's sarcoma (332), but further studies have not supported a role for *M. penetrans* in this condition (101, 284) and it has since been detected in persons who are not infected with human immunodeficiency virus (336). *M. penetrans* may be found in the urethra, rectum, and throat of homosexual men (290). Antibodies against *M. penetrans* were detected in up to 40% of human immunodeficiency virus-positive persons, in contrast to less than 1% of human immunodeficiency virus-negative persons (101, 331). Thus far there is no compelling evidence that this mycoplasma causes significant disease in any population despite the fact it possesses some features present in other pathogenic mycoplasmas that might enable it to do so under favorable circumstances, such as a prominent terminal tip structure that confers its ability to invade epithelial cells (23, 28). Rottem has discussed the interaction of *M. penetrans* with host cells in a comprehensive review (239). No data are available for pregnant women or neonates.

Mycoplasma pirum

M. pirum was characterized in 1985 (75), but its natural host was unknown (75). Renewed interest in *M. pirum* came about during the early 1990s during the time when mycoplasmas were being actively studied as possible cofactors in human immunodeficiency virus-related disease, when Montagnier and Blanchard isolated this mycoplasma from peripheral blood lymphoid cells of human origin (197). However, subsequent studies did not detect the organism in peripheral blood mononuclear cells in persons with or without human immunodeficiency virus infection (156). It was not detected in the urethras of men with urethritis (72); but it was found by PCR in the rectums of five homosexual men (290). *M. penetrans*, *M. pirum*, *M. fermentans*, and *M. genitalium* were isolated from urine of patients with AIDS who had severe immunodeficiency more often than from that of persons who were human immunodeficiency virus negative (126). Despite the presence of *M. pirum* as a colonizer in the settings described above, no conclusive proof that this mycoplasma is independently pathogenic in humans has been offered thus far and no data for neonates or pregnant women are available.

Mycoplasma pneumoniae

M. pneumoniae is the best known and most intensely studied human mycoplasma. Its role in human disease was reviewed recently in this journal (325). Since *M. pneumoniae* is primarily a cause of respiratory tract infections in children and adults, it beyond the scope of this review to discuss its biology and disease associations in depth. However, it is worth mentioning that this mycoplasma has been isolated from the lower urogenital tract of women (99) and infants sometimes experience mycoplasmal respiratory tract infection that is transmitted from person to person in the community setting. Investigators in Boston were unable to isolate this mycoplasma from the nose, throat, external ear canal, genitalia, conjunctivae, blood,

urine, or CSF in 1,500 infants (44), but this was done in the days prior to the availability of more sensitive methods of detection, such as the PCR assay. Many women of childbearing age have respiratory infections caused by *M. pneumoniae*, and there has been one report (304) of *M. pneumoniae* documented by PCR in the nasopharyngeal aspirate of a neonate with congenital pneumonia, suggesting transplacental acquisition may have occurred. This finding justifies the need for further study of *M. pneumoniae* as an agent of respiratory disease in neonates.

LABORATORY DIAGNOSIS

Culture

There are insufficient data to make specific recommendations related to indications for diagnosis and treatment of ureaplasmal infection of the chorioamnion. It is obvious from available data that routine culture of the cervix and/or vagina is not indicated because of the commonplace finding of these organisms in healthy women. Culture of amniotic fluid alone is unreliable for detection of chorioamnion infection because only a portion of those with ureaplasma-positive cultures of the chorioamnion will also have positive culture of the amniotic fluid. The fact that analysis by the PCR assay also indicates a much lower frequency of infection in amniotic fluid than in the chorioamnion confirms that sole reliance on analysis of amniotic fluid will lead to underdiagnosis of chorioamnion infection and hence chorioamnionitis.

Routine screening of healthy neonates is not indicated since many of them are colonized. However, if there is clinical or radiological evidence of respiratory distress, pneumonia, meningitis, or overall instability, particularly if no other bacterial cultures are positive and in whom there are no other obvious etiologies, infection with the genital mycoplasmas should be considered. Detection of mycoplasmal or ureaplasmal infection in amniotic fluid, placental tissue, normally sterile sites such as blood or CSF, or in the upper or lower respiratory tract can be achieved by culture using appropriate techniques. Clinicians who are interested in obtaining a microbiological diagnosis of infection in a pregnant women or neonate should ascertain whether their hospital laboratory is equipped to perform the cultures on-site or whether they must be shipped to a reference laboratory.

The fastidious nature and susceptibility of these organisms to drying and other adverse environmental conditions mandate that careful attention be given to specimen collection, inoculation of transport medium at bedside whenever possible, and proper transportation and shipping conditions if organisms are to remain viable. Details of specimen requirements, collection, shipping, processing, and interpretation of results are described in detail elsewhere (312, 321, 322). Cumitech 34 (312) provides an up-to-date summary of all aspects of laboratory diagnosis of mycoplasmal and ureaplasmal infections.

Although culture is considered the reference standard for detection of *M. hominis* and *Ureaplasma* spp., it is expensive and requires specialized media and expertise that are not widely available outside of larger medical centers or mycoplasma research or reference laboratories. Confirmed culture results can usually be available within 2 to 5 days, exclusive of specimen transport time and shipment if an offsite reference laboratory is used. Ureaplasmas can be positively identified to genus level by their colonial morphology and urease production, as shown in Fig. 3. In contrast, mycoplasmal species such as such as *M. hominis* that produce fried-egg colonies on A8 or SP4 agar (Fig. 4) may be presumptively identified based on growth rates, hydrolysis of arginine, and body site of origin, but definitive species identification requires additional tests, which have historically included growth inhibition using homologous antisera, immunoblotting with monoclonal antibodies, colony epi-immunofluorescence, and, more recently, the PCR assay (322).

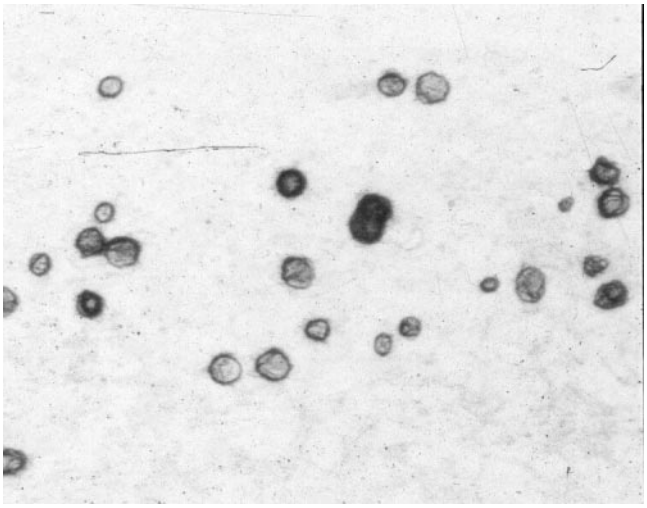

FIG. 3. Colonies of *Ureaplasma* spp. growing on A8 agar after 48 h of incubation as they appear under 126× magnification using a stereomicroscope. Colonies are typically 15 to 30 μm in diameter and have a brownish appearance due to urease activity in the presence of the $CaCl_2$ indicator contained in the agar.

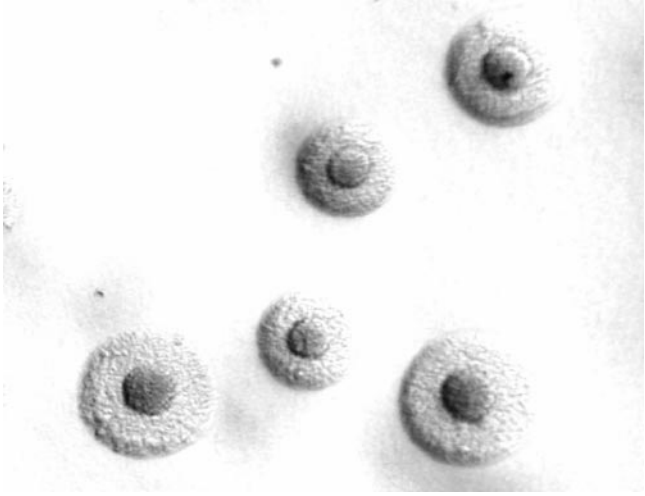

FIG. 4. Colonies of *Mycoplasma hominis* growing on A8 agar after 72 h of incubation as they appear under 126× magnification using a stereomicroscope. Colonies are typically 200 to 300 μm in diameter and demonstrate a characteristic fried-egg appearance.

Nucleic Acid Amplification

Considerable attention has been given in recent years to the application of the PCR assay in primary detection of mycoplasmal and ureaplasmal perinatal infections. PCR is essential if fastidious, slow-growing organisms such as *M. genitalium* or *M. fermentans* are sought and is also valuable in differentiating ureaplasmal species and serotypes, as described earlier. Gene targets for PCR assays used to detect ureaplasmas have included the urease gene (30), 16S rRNA genes (238), and the multiple-banded (MB) antigen gene (200, 294).

PCR assays for *M. hominis* have used 16S rRNA and ribosomal DNA as the gene targets (100, 344). The theoretical advantages of the PCR assay for detection of genital mycoplasmas include the fact that no viable organisms are necessary, its limit of detection is much better than culture, and results can be available in 1 day. Most studies evaluating the PCR assay for detection of mycoplasmas in clinical specimens have compared the technique to culture for calculation of sensitivity and specificity. As has been the case with other fastidious microbes such as chlamydiae, this approach may not be completely valid since culture is never going to be able to detect their presence as readily as nucleic acid amplification when performed properly using appropriate primers and in the absence of inhibitors. Several recent studies have compared culture with the PCR assay for detection of genital mycoplasmas in samples from pregnant women, neonates and a variety of other conditions. Since the focus of this review is perinatal infections, commentary is limited to studies addressing this topic. A recent review by Colaizy and colleagues (55) provides a timely critique of the application of the PCR assay in all facets of mycoplasmology.

Blanchard and coworkers (30) identified 10 of 293 amniotic fluid specimens that were positive for *Ureaplasma* spp. by PCR, four of which were also culture positive. There were no specimens that were PCR negative and culture positive. The ability of the PCR assay to detect ureaplasmas in female genitourinary specimens, including cervices, amniotic fluid, and vaginal specimens, has been shown to be comparable or superior to that of culture according to multiple studies (5, 30, 55, 180, 341).

The PCR assay has also been evaluated as a diagnostic tool for rapid detection of ureaplasmal infection in neonates with lower respiratory infections as well as to aid in the elucidation of the possible role of these organisms in BPD. The first report of the PCR assay used for detection of ureaplasmas in endotracheal aspirates of neonates occurred in 1992. Scheurlen et al. (254) were able to detect only one PCR-positive specimen among 36 ventilated neonates studied. Blanchard et al. (30) found 99% agreement between PCR analysis and culture in 95 endotracheal aspirate samples. Only one specimen was positive by culture and not by PCR assay. Other investigations have shown agreements of PCR to be 91 to 95% in comparison to culture (61, 200).

A major concern when considering the results of any study in which PCR is compared to the inherently less sensitive culture technique is how to interpret findings in which the PCR is positive and the culture is negative to evaluate the specificity of the PCR assay and ensure the results were not due to a false-positive reaction due to contamination. Use of a second gene target and/or assessing repeat specimens may help to resolve such cases but this has not been done consistently in the studies published to date. It is also important to emphasize that the sensitivity of culture in detecting ureaplasmas in tracheal aspirates may vary considerably with the experience of the laboratory performing the culture and the methods of culture used. We determined through a retrospective review of neonatal respiratory cultures that limiting cultures to agar-based methods and omission of broth cultures and serial dilutions will result in a lower isolation rate (314).

Multiplex PCR systems have also been described and applied to the detection of genital mycoplasmas in clinical specimens with favorable results in comparison to culture (269). Despite the overall favorability in studies comparing PCR with culture for detection of *M. hominis* and *Ureaplasma* spp., this technique is not commercially available in the United States and has been limited to research laboratories or specialized molecular diagnostic reference laboratories. Until technology is advanced to the point that PCR assays for genital mycoplasmas can be purchased commercially in a kit format by diagnostic laboratories, it is unlikely to gain widespread usage for routine microbiological diagnosis. Real-time PCR has been adapted for quantitation and characterization of ureaplasmal isolates to species level (184). The high yield and relative simplicity of cultivation in agar and broth media for rapidly growing organisms such as *Ureaplasma* spp. and *M. hominis* supports the concept that culture should remain an important part of the diagnostic process. Specimen types such as blood which may contain a very low concentration of microbes in a huge background of human DNA may not be ideal for PCR.

Serology

There has been interest for a number of years in development of serological assays for detection of the host immune response to genital mycoplasmas. However, their ubiquity in the urogenital tracts of adults makes interpretation of antibody titers difficult, and the mere existence of antibodies alone cannot be considered significant in most circumstances. However, when invasive extragenital disease occurs, elevation of antibody titers is often apparent in immunocompetent hosts. The unique susceptibility of hypogammaglobulinemic persons to invasive infections due to *Ureaplasma* spp. testifies to the importance of the humoral immune response for protection against disease due to this organism (288). Although it has been suggested that type-specific antibody titer rises against certain ureaplasmal serovars occur in women with pregnancy wastage and in infants with respiratory disease compared to control patients, more comparative data from well-characterized and carefully matched control populations are needed to fully appreciate the value of antibody determination in these settings.

Serological tests for *M. hominis* and *Ureaplasma* spp. using the techniques of microimmunofluorescence, metabolism inhibition, and enzyme immunoassay have been developed and used in research settings (36, 37, 282, 285), but no assays for genital mycoplasmas have been standardized and made commercially available in the United States. Thus, they remain primarily research tools and cannot be recommended for routine diagnostic purposes at present.

TABLE 4. MICs of various antimicrobials for *Mycoplasma hominis*, *Ureaplasma* spp., and *Mycoplasma genitalium*[a]

Antimicrobial	MIC (μg/ml)		
	M. hominis	*Ureaplasma* spp.	*M. genitalium*
Tetracycline	0.2–2[b]	0.05–2[b]	≤0.01–0.05
Doxycycline	0.1–2[b]	0.02–1[b]	≤0.01–1
Erythromycin	32–>1,000	0.02–16	≤0.01
Roxithromycin	>16	0.1–2	0.01
Diithromycin	>64	0.25–2	≤0.015–0.12
Clarithromycin	16–>256	≤0.004–2	≤0.01
Azithromycin	4–64	0.5–4	≤0.01
Cethromycin	≤0.008–0.031	≤0.008–0.031	NA
Telithromycin	2–16	≤0.015–0.06	≤0.015
Josamycin	0.05–2	0.5–4	0.01–0.03
Clindamycin	≤0.008–2	0.2–64	0.2–1
Lincomycin	0.2–1	8–256	1–8
Pristinamycin	0.1–0.5	0.1–1	≤0.01–0.02
Spiramycin	32–>64	4–32	0.12–1
Chloramphenicol	4–25	0.4–8	0.5–4
Gentamicin	2–16	0.1–13	NA
Ciprofloxacin	0.1–4	0.1–16	2
Ofloxacin	0.1–64	0.2–25	1–2
Levofloxacin	0.1–2	0.2–2	0.5–1
Sparfloxacin	<0.008–0.1	0.003–1	0.05–0.1
Gatifloxacin	0.016–0.25	0.125–1	≥0.125
Moxifloxacin	0.06–0.12	0.12–0.5	0.03–0.06
Gemifloxacin	0.0025–0.06	0.03–0.5	0.05–0.125
Garenoxacin	0.008–0.063	0.016–1	0.06–0.125
Rifampin	>1,000	>1,000	NA
Quinupristin/dalfopristin	0.25–8	0.12–0.5	0.05
Nitrofurantoin	6–500	13–>1,000	NA

[a] Data were compiled from multiple published studies in which different methodologies and often different antimicrobial concentrations were used. NA, not available.
[b] Tetracycline-susceptible strains only.

ANTIMICROBIAL SUSCEPTIBILITY

The types of antimicrobial agents currently available for treatment of ureaplasmal and mycoplasmal infections in neonates is limited and when treatment is rendered it usually given without guidance of antimicrobial susceptibility testing. From a practical standpoint, antimicrobial susceptibility testing for these organisms is mainly of value for serious infections such as meningitis, evaluation of new drugs for in vitro activities, or for surveillance purposes to monitor development of resistance.

Methods for antimicrobial susceptibility testing by microbroth and agar dilution have been described (312, 321, 322) but thus far, there have not been standardized procedures published by the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards), although the Mycoplasma Subcommittee is actively working to develop standardized testing conditions and quality control reference ranges for drugs that may be used to treat infections caused by these microorganisms.

MICs for antimicrobial agents suitable for use in treatment of mycoplasmal or ureaplasmal infections are shown in Table 4. Since mycoplasmas and ureaplasmas lack peptidoglycan, they are not affected by beta-lactams or vancomycin. They are not susceptible to sulfonamides or trimethoprim because they do not synthesize folic acid. However, they are generally susceptible to certain antibiotics that interfere with protein synthesis, such as tetracyclines. While ureaplasmas are generally susceptible to macrolides, they are resistant to lincosamides except in high concentrations. *M. hominis*, in contrast, is naturally resistant to erythromycin in vitro, but susceptible to 16-membered macrolides (josamycin and miocamycin) and lincomycin. Furnieri (88) determined that the genetic basis for macrolide resistance in *M. hominis* is due to mutations in genes corresponding to the loop of the peptidyl transferase (domain V) in 23S rRNA. Despite a report of high-level erythromycin resistance in ureaplasmas in the 1980s (211), it is our belief that such resistance to macrolides in these organisms is extremely uncommon, if indeed it occurs at all, and no mechanism for macrolide resistance in ureaplasmas has been verified at the ribosomal level.

Our experience has been that results of susceptibility testing of this organism are subject to influence by a number of environmental factors that may result in falsely elevated MICs. These include release of urea into the atmosphere of microtiter plates, effectively raising the pH and possibly affecting neighboring wells unless each well is sealed during incubation of broth microdilution test systems, and the effect of an acidic growth medium necessary for ureaplasmal growth on the in vitro activity of macrolides. Data from over 300 clinical isolates of *Ureaplasma* spp. obtained from urethral or cervical specimens of men and women from a broad geographic area tested in the Diagnostic Mycoplasma Laboratory at the University of Alabama at Birmingham showed erythromycin MICs ranging from 0.125 to 8 μg/ml with a MIC_{90} of 2 μg/ml (44). MIC_{90} values for the newer macrolides, azithromycin and clarithromycin, against ureaplasmas are 1 μg/ml and 0.063 μg/ml, respectively (315).

Some mycoplasma and ureaplasma isolates may be susceptible to streptomycin or other aminoglycosides, but not predictably so and there is no evidence these agents are effective in vivo. Fluoroquinolones such as levofloxacin, moxifloxacin, gatifloxacin, and gemifloxacin are active against mycoplasmas and ureaplasmas in vitro, but their roles as therapeutic agents have not been established in pediatrics because of potential effects on cartilage development.

Acquisition of the *tetM* determinant that mediates tetracycline resistance was described in *Ureaplasma* species and *M. hominis* in the 1980s (231, 232). To date, this is the only mechanism of tetracycline resistance described in these organisms. The frequency of tetracycline resistance in genital mycoplasmas is probably influenced by factors such as geography, antibiotic pressure and sexual promiscuity in adults. The occurrence of resistant organisms in neonates should logically reflect that of their mothers since the organisms are acquired by vertical transmission. Tetracycline resistance in *M. hominis* has been reported to occur in as many as 40% of clinical isolates and in ureaplasmas it has been reported to occur in approximately 10% (44), but few studies have been performed in recent years to determine whether these numbers are still valid and they are probably quite variable from place to place and among different patient populations.

We recently evaluated antimicrobial susceptibility data for 100 unique isolates of *Ureaplasma* spp. obtained from a broad geographic area of the United States over the 5-year period from 2000 to 2004. There were 45 isolates proven to have *tetM* by PCR, indicating a substantially greater proportion of these

organisms now has reduced susceptibility to tetracycline when compared to earlier reports.

Naturally occurring resistance to fluoroquinolones has been reported in genital mycoplasmas isolated from adults in France (24) that was mediated by mutations in DNA gyrase and topoisomerase IV, presumably as a result of selective pressure due to widespread use of these drugs. High-level fluoroquinolone resistance in an isolate of *U. parvum* containing the expected mutations detected in a vaginal specimen from a patient in Ohio who had chronic cystitis and who had received prolonged treatment with levofloxacin was encountered in our laboratory in 2004, proving this resistance also occurs in North America.

THERAPEUTIC CONSIDERATIONS

Treatment of Respiratory and Systemic Infections

Among the limited options, macrolides are the most promising antimicrobial agents currently available for use in neonatal ureaplasmal and mycoplasmal infections. Due to its toxicity, doxycycline is not a realistic therapeutic alternative except for ill infants from whom *U. urealyticum* or *M. hominis* is isolated from the CSF. Clindamycin has also been used successfully to treat systemic infections in infants caused by *M. hominis* (1).

Making specific recommendations for treating genital mycoplasma infections in pregnant women or neonates is particularly difficult in view of the fact that the spectrum of ureaplasmal disease in these populations has not been fully described and there are very few clinical studies indicating in vivo efficacy of antibiotics. Therefore, not only is choice among the limited drug options controversial, but also the actual indications concerning conditions under which treatment should be offered, dosage and duration of therapy are debatable.

Ureaplasmas can frequently be isolated from the upper respiratory tracts of neonates, but there is no evidence that cultures should be obtained routinely in the absence of symptomatic disease. Neonates clinically ill with pneumonitis or showing signs of central nervous system disease, particularly progressive hydrocephalus with or without CSF pleocytosis, for whom bacterial cultures are negative or in whom there is no improvement with antibiotic therapy may warrant specific cultures of blood, respiratory secretions, pleural fluid, and CSF for *Ureaplasma* spp. and *M. hominis* and treatment if cultures are positive.

Data concerning pharmacokinetics, microbiological efficacy, and safety of macrolides antimicrobials in preterm neonates are scant. Differences in body composition, drug distribution, protein binding, biotransformation, hepatic and renal excretion dictate that data from term infants and older children cannot be universally extrapolated to the preterm population (221).

Waites et al. studied the pharmacokinetics and microbiological efficacy of intravenous erythromycin in preterm neonates colonized in the lower respiratory tract with *Ureaplasma* spp (324). Fourteen preterm neonates with birth weights of ≤1,500 g who were ≤15 days of age and who required supplemental oxygen and/or mechanical ventilation from whom ureaplasmas were isolated from the lower respiratory tract were enrolled into the study. Neonates were randomized to receive erythromycin lactobionate, either 25 or 40 mg/kg/day, in four divided doses given at 6-hour intervals for up to 10 days. Blood samples collected at multiple time points after the initial and steady-state doses were assayed for erythromycin by liquid chromatography. Follow-up cultures of tracheal aspirate were performed on days 5 to 7 of treatment in neonates who were still intubated at that time. Erythromycin MICs for the ureaplasmal isolates ranged from 0.031 to 2 μg/ml. Eleven neonates completed ≥7 days of treatment. Serum erythromycin concentrations met or exceeded most MICs, with peak values of 3.05 to 3.69 and 1.92 to 2.9 μg/ml for the 40- and 25-mg/kg/day dosage groups, respectively. Nine of 10 (90%) follow-up cultures were negative. No adverse effects thought to be related to administration of erythromycin were observed with either dosage.

This pilot study provided data supporting the use of 40 mg/kg/day of erythromycin for intravenous treatment of preterm neonates. However, measurement of erythromycin concentrations in bronchial secretions would provide important data if such specimens can be obtained. Additional data regarding pharmacokinetics and dosage recommendations for oral erythromycin in infants under 4 months of age was reported by Patamasucon et al. (213) in a study of infants being treated for pertussis or chlamydial infections. They proposed that erythromycin estolate suspension could be given at a dosage of 30 mg/kg/day in 3 divided doses or 20 mg/kg/day in 2 divided doses and that erythromycin ethylsuccinate could be given at a dosage of 40 mg/kg/day in 4 divided doses.

There is some concern over use of erythromycin in infants because of an association with hypertrophic pyloric stenosis (249), cardiac toxicity (84), and the possibility of hepatotoxicity. A comparison of 33 infants who received intravenous erythromycin for treatment of ureaplasmal infections with 176 matched infants who did not receive this drug showed no evidence of hearing abnormalities, elevated hepatic enzymes or bilirubin, or thrombophlebitis (317). An earlier study of 87 preterm infants (40) who received up to 14 days of oral erythromycin estolate (40 mg/kg/day) also found no evidence of toxicity. Erythromycin is now used much less often in older children and adults due to the availability of newer macrolides such as clarithromycin and azithromycin which allow more convenient once daily dosage and better tolerability. Whether the same risks of toxicity exist with the newer macrolides in neonates is not known.

Treatment of invasive mycoplasmal and ureaplasmal infections of the central nervous system are particularly problematic in infants due to the limited options available. In view of poor CSF penetration by erythromycin, tetracyclines are probably the most effective drugs available for ureaplasmal or mycoplasmal infections of the CSF. It may be prudent to observe stable, asymptomatic infants and to document persistent infection through follow-up CSF cultures before treatment with these potentially toxic antibiotics is initiated since some CSF infections have resolved spontaneously (199, 320, 323). In vitro susceptibilities should also be obtained if tetracyclines are used because of the possibility of resistance to this class of antimicrobials.

Since clinically useful antibiotics are only mycoplasmastatic, not mycoplasmacidal, the immune status of the premature infant might well be a crucial component in any successful drug treatment. Experience in treatment of chronic ureaplasmal

and mycoplasmal arthritis in hypogammaglobulinemic patients clearly suggests that this is the case (288, 310, 334). Although there are no established guidelines, limited clinical experience with neonates and other persons with systemic infections due to *U. urealyticum* suggests that a minimum of 10 to 14 days of treatment is best. Whether the intravenous or oral route with erythromycin, doxycycline, or alternatives is employed depends on the overall condition of the patient and the nature of the infection being treated. Follow-up cultures of the infected site to document microbiologic efficacy of the drug are suggested when clinical improvement does not occur.

Garland and Murton (91) eradicated *Ureaplasma* spp. from CSF with a combined 14-day regimen of intravenous erythromycin and chloramphenicol. Waites et al. (323) reported successful treatment of CSF infection with doxycycline alone in one infant. An additional infant was given erythromycin for 10 days after a treatment failure with 14 days of doxycycline. A fourth infant who had both a positive CSF culture and ureaplasmal pneumonia was treated successfully with intravenous erythromycin alone for 14 days. However, Shaw et al. (257) described an infant from whom *Ureaplasma* spp. was isolated in the CSF over 16 weeks despite a protracted course of erythromycin. Eradication was finally achieved with doxycycline. Though it is now rarely used in any patient population in developed countries because of toxicities, chloramphenicol has been used successfully to treat *M. hominis* infections of the central nervous system in neonates (149).

Antimicrobial Treatment for Association of Ureaplasmas with BPD

The accumulating evidence implicating *Ureaplasma* spp. in BPD has led to the performance of several macrolide treatment trials to address causality (Table 5). In addition to the antibacterial effects of erythromycin and other macrolides, these drugs may exert anti-inflammatory properties independently of their effect on bacterial metabolism. This aspect makes them especially attractive for therapeutic intervention in a chronic inflammatory condition such as BPD, but it may also make assessment of the role of an infectious organism more complex.

Specifically, the macrolides as a class inhibit neutrophil migration by reducing IL-6, IL-8, and ICAM-1 production by bronchial epithelial cells and may also have an immunomodulatory effect on neutrophils by their antioxidant effects and modulation of gene transcription of proinflammatory cytokines (172, 278). Macrolides also decrease mucus secretion in the airways (279). The appropriate treatment of neonates with BPD who are culture positive for *Ureaplasma* spp. may involve eradication of the ureaplasmas by antibiotics, modulation of the immune response by steroids, and/or administration of antioxidants. Until the mechanism of disease production is known, therapy type and the need for it will need to be based on the judgment of each individual clinician on a case-by-case basis.

Although no adequately powered multicenter prospective clinical trials with any of the macrolides have been performed thus far, some smaller investigations utilizing erythromycin to treat infants from whom ureaplasmas were detected in the lower respiratory tract have been reported. Walsh et al. (327) treated three infants with BPD who had proven ureaplasmal infection based on lung biopsy. Improvement was noted after therapy directed at *Ureaplasma* even though two of them remained culture positive. The significance of these findings is difficult to assess because of the very small numbers and additional use of doxycycline in some of the infants.

The results of 10 other studies are summarized in Table 5. Most of them were very small and did not involve a systematic randomization of infants to receive erythromycin. Two small randomized prospective controlled studies of erythromycin therapy aimed at prevention of BPD in preterm infants have been reported. Lyon et al. (183) randomly treated infants before culture results were known and found that isolation of ureaplasmas was associated with tracheal inflammatory responses, but erythromycin treatment was not associated with a reduction in the incidence or severity of BPD. Jonsson et al. (135) administered erythromycin to infants known to be culture positive for *Ureaplasma* spp. and determined that the antibiotic reduced colonization but did not significantly alter the length of time that supplemental oxygen was required. The ORACLE study (143), which evaluated the use of antepartum broad-spectrum antibiotics for premature rupture of fetal membranes, showed a slight benefit for the baby if the mother received erythromycin. While there was no reduction in chronic lung disease alone, defined as oxygen dependence at 36 weeks of gestation, there was improvement in the composite outcome, which included BPD as one of the components. The results from this trial suggest that early antimicrobial treatment may interrupt the inflammatory cascade that leads to lung disease and development of BPD.

In general, the studies summarized in Table 5 have shown that treatment with erythromycin will sometimes, but not always, eradicate ureaplasmas from the lower respiratory tract but no significant effect on respiratory outcome has been conclusively shown in any of them. However, the small sample sizes, uncontrolled experimental designs, various gestational ages and birth weights, differences in use and duration of mechanical ventilation, and widely ranging times after birth until treatment was initiated make it impossible to draw meaningful conclusions about the value of macrolide treatment to eradicate ureaplasmas from the respiratory tract of preterm infants or impact their respiratory outcomes.

Insight gained from previous intervention trials in human neonates may influence the design of any intervention that attempts to reduce BPD by treatment of *Ureaplasma*. Such a study, in order to fully evaluate whether a causal relationship exists between colonization of preterm neonates by *Ureaplasma* and development of BPD, needs to be a large, multicenter therapeutic trial. Because of the heterogeneity of effect size in previous observational studies, a power analysis based on the available observational data is not reliable. Therefore, prior to a pivotal study for efficacy of treatment, proof of concept should be established in a smaller trial. The antibiotic used must be able to eradicate the organism from the respiratory tract and have an acceptable safety profile. Timing of treatment may be crucial. As infection with *Ureaplasma* spp. leads to a proinflammatory state, early treatment and eradication of the organism may be necessary to interrupt the inflammatory cascade leading to the development of BPD. Later

TABLE 5. Clinical studies of intravenous erythromycin for treatment of *Ureaplasma* respiratory tract infections in infants[a]

Reference	Erythromycin dosage and route[b] (mg/kg/day)	Duration of treatment (days)	No. and type of subjects	Outcomes and/or comments
Abele-Horn (3)	24–45, i.v.	9–14	5 infants <1,420 g birth weight	All 5 infants had BPD. Treatment resulted in an improved clinical course. No follow-up cultures were performed.
Baier (19)	40, i.v.	5 or 10	17 infants ≤1,160 g birth weight	This uncontrolled study was designed to assess eradication in tracheal secretions. Decision to treat was at the discretion of physician. 6/11 (55%) infants recultured after 15 days were positive. There was a trend towards an increased incidence of BPD in infants with persistence of *Ureaplasma* spp.
Bowman (34)	20, i.v.	7	19 infants <1,000 g birth weight	Among 19 culture-positive infants treated, 4 required a second course of treatment before tracheal cultures were negative. There was no difference in rate of BPD, duration of oxygen therapy, or time until discharge among treated infants who were culture positive in comparison to 102 culture-negative infants who were not treated.
Heggie (112)	20–50, i.v.	7–14	10 infants ≤1,000 g birth weight	Decision to treat was at the discretion of the physician. No significant differences were noted in development of BPD among infants who were culture positive in the trachea versus 20 infants who were culture negative. No follow-up cultures were performed.
Izraeli (128)	40, p.o.	10	3 infants ≤952 g birth weight	Ureaplasmas were not recovered during treatment but reappeared in tracheal secretions following cessation of therapy in two infants. One infant died from respiratory failure. No changes in clinical course were noted during treatment.
Jonsson (135)	40, p.o. or i.v.	10	14 infants ≤1,728 g birth weight	Infants culture-positive in trachea or nasopharynx were randomly treated. 12/14 had negative cultures posttreatment. One infant became negative after a second i.v. course of erythromycin. 8 infants who were not treated remained culture positive 2 weeks after initial culture. Treated infants did not differ from untreated infants with regard to duration of supplemental oxygen or development of BPD.
Lyon (183)	15, i.v.	7	34 infants ≤2,300 g birth weight	Infants were randomized to receive treatment before culture results were known. 9 were ureaplasma positive in trachea. Treatment did not affect cytokine levels or development or severity of BPD. No follow-up cultures were performed.
Mhanna (196)	Not stated	7–19	38 infants ≤975 g birth weight	This was a retrospective uncontrolled evaluation of infants with tracheal cultures positive for *Ureaplasma* spp. who were treated at the discretion of the physician. Treatment was not begun until an average of 2 weeks after birth. Treatment had no effect on BPD. No follow-up cultures were performed.
Pacifico (209)	Not stated	7–14	10 infants ≤1,500 g birth weight	Decision whether to treat was left to the physician. BPD occurred in 7/10 (70%) treated infants who were culture positive in the trachea versus 4/6 (66.7%) in untreated infants. Treated infants were of significantly lower gestational age, so the two groups were not truly comparable. No follow-up cultures were performed.
Waites (324)	25–40, i.v.	7–10	14 infants ≤1,500 g birth weight	This study was designed to assess eradication and relate serum drug levels to bacteriologic outcomes. 9/10 (90%) infants who received at least 7 days of treatment were culture negative in the trachea 3 to 4 days after the final dose.

[a] The studies listed are those published in journals indexed in the National Library of Medicine for which sufficient information was provided for meaningful evaluation and only one drug (erythromycin) possibly affecting ureaplasmas was administered. Individual case reports were not included.

[b] i.v., intravenous; p.o., per os.

treatment may be insufficient reverse the inflammatory process while subjecting the infant to risks of the antibiotic.

The ideal study would involve a randomized placebo-controlled trial in which treatment would be initiated immediately after birth before pulmonary damage can worsen, with adequate follow-up testing to measure eradication and clinical outcomes. However, the fact that some ureaplasmal infections and initiation of an inflammatory response may occur in utero could complicate the interpretation of findings of such a study. Consideration should be given to use of one of the newer macrolides such as azithromycin or clarithromycin in view of their improved pharmacokinetics and better penetration of lung tissues. These agents may be expected to be as good as or possibly better at eradication of organisms from the airways as erythromycin, but the safety of their use has not been systematically evaluated in newborn infants. Demonstration that macrolide treatment initiated in very low birth weight preterm neonates soon after birth can reduce the incidence and/or severity of BPD would have an enormous impact on long-term health of such infants and save vast amounts of health care costs even if it does not conclusively prove that *Ureaplasma* spp. are primary causes of this condition.

CONCLUDING REMARKS

The ability of *Ureaplasma* spp. and *M. hominis* to cause pneumonia, bacteremia, and meningitis in newborns can no longer be questioned. There is strong evidence that ureaplasmas induce an inflammatory response in utero that can result in chorioamnionitis and chronic lung injury in neonates. The association of *Ureaplasma* spp. with BPD has been supported by the majority of observational studies, but proof of causality is still lacking. Whether antimicrobial treatment of ureaplasma-colonized infants can effectively eradicate these organisms and reduce the incidence of BPD will require a large, multicenter, randomized treatment trial. The availability of powerful molecular diagnostic tools to complement culture for the detection and characterization of ureaplasmas in clinical specimens has enabled the designation of the two *Ureaplasma* biovars as individual species, but additional work must be done to establish whether there is differential pathogenicity between the *Ureaplasma* spp. The role of *Ureaplasma* spp. in preterm labor, the frequency and morbidities associated with genital mycoplasmas in systemic diseases in neonates, and the relationship of host immune status to successful therapy all warrant further investigation.

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