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Current Status of the Mollicute (*Mycoplasma*) Lung Disease: Pathogenesis, Diagnostics, Treatment and Prevention

Silvia Giono-Cerezo^{1,*}, Guadalupe Estrada-Gutiérrez²,
José Antonio Rivera-Tapia³, Jorge Antonio Yáñez-Santos³
and Francisco Javier Díaz-García⁴

¹Departamento de Microbiología, Escuela Nacional de Ciencias Biológicas, IPN

²Departamento de Infectología, Instituto Nacional de Perinatología, México, D.F.,

³Benemérita Universidad Autónoma de Puebla, Puebla, México

⁴Departamento de Salud Pública, Facultad de Medicina, UNAM
México

1. Introduction

The microorganisms referred as mycoplasmas ("mushroom form") are eubacteria included within the Class Mollicutes (from latin *mollis* = "soft", *cutis* = "skin"), which comprises the smallest self-replicating bacteria, showing distinctive features such as: a) lack of a rigid cell wall envelope, b) sterol incorporation into their own plasma membrane, and c) Reduced cellular (0.3 - 0.8 μm diameter) and genome sizes (0.58-2.20 Mb). Some genera use the UGA stop codon to encode tryptophan [Bove, 1993; Razin et al., 1998].

The term "mycoplasmas" will be used herein when referring to any species within the Class *Mollicutes*. Due to their reduced genome sizes, the mycoplasmas exhibit restricted metabolic and physiological pathways for replication and survival [Razin et al., 1998]. This makes evident why these bacteria display strict dependence to their hosts for acquisition of aminoacids, nucleotides, lipids and sterols as biosynthetic precursors. [Baseman & Tully, 1997; Razin et al., 1998].

Recognized human pathogenic mycoplasma species mostly belongs to the *Mycoplasma* and *Ureaplasma* genera (Table 1). Acute or fulminant diseases are rarely caused by these bacteria, instead they produce subclinical or covert infections that become chronic and/or persistent [Baseman & Tully, 1997; Razin et al., 1998]. Cell surface colonization and in some cases subsequent invasion and intracellular residence have been well documented for several *Mycoplasma* species which infect humans [Andreev et al., 1995; Baseman et al., 1995; Díaz-García et al., 2006; Giron et al., 1996; Jensen et al., 1994; Lo et al., 1993; Taylor-Robinson et al., 1991].

The primary habitats of the mycoplasmas infecting humans are the mucosal surfaces of the respiratory and genitourinary tracts [Cassell et al., 1994a; Taylor-Robinson, 1996]. Moreover,

* Corresponding Author

the mycoplasmas display host- and tissue-specific tropism, reflecting their nutritional demands and parasitic lifestyle [Razin et al., 1998]. Thus, *M. pneumoniae* is found principally in the respiratory tract, whereas *M. genitalium*, *Ureaplasma spp.*, *M. hominis*, *M. fermentans* and *M. penetrans* are primarily urogenital residents, but exceptionally they can be isolated from other unusual tissues and organs, especially in immunocompromised patients or in patients undergoing solid organ transplantation [Waites & Talkington, 2004; Waites et al., 2005; Waites, 2008].

Mycoplasma respiratory infections in humans can be ascribed mainly to *M. pneumoniae* and, in fetuses or newborns, to *Ureaplasma* species. *M. pneumoniae* is a well-known pathogen in atypical and community-acquired pneumonia, whereas *U. urealyticum* and *U. parvum* have been associated with vertically-transmitted intrauterine and neonatal pneumonia [Taylor-Robinson, 1996; Waites et al., 2005].

Species	Primary colonization sites		Substrate utilization		
	Oropharyngeal tract	Urogenital tract	Glucose	Arginine	Urea
<i>Mycoplasma fermentans</i>	✓	✓	✓	✓	✗
<i>M. genitalium</i>	✓	✓	✓	✗	✗
<i>M. hominis</i>	✓	✓	✗	✓	✗
<i>M. penetrans</i>	✗	✓	✓	✓	✗
<i>M. pneumoniae</i>	✓	✗	✓	✗	✗
<i>Ureaplasma parvum</i>	✓	✓	✗	✗	✓
<i>U. urealyticum</i>	✓	✓	✗	✗	✓

✓ Present; ✗ Absent

Modified from Taylor-Robinson, 1996.

Table 1. Mycoplasma species pathogenic for humans.

A worldwide rise in the frequency of *M. pneumoniae*-associated lower respiratory tract disease has been observed, from 6 - >30% in the 1990s, to 0 - 66.7% in 2010 [Reviewed by Loens et al., 2003, 2010]. Therefore the pathogenic role of *M. pneumoniae* in respiratory disease has been proved in persons of all ages, sometimes causing severe respiratory disease, and it may induce clinically significant manifestations in extrapulmonary sites by direct invasion and/or immunologic effects. Only in the USA, *M. pneumoniae* is responsible for more than 100,000 hospitalizations of adults each year [Waites & Talkington, 2004; Waites, 2008]. This close interplay between *M. pneumoniae* and the host's respiratory epithelium induces local damage and in turn elicits release of inflammatory mediators by the host. The magnitude of the later response appears to be related to the severity of disease [Waites, 2008].

Respiratory tract colonization with *Ureaplasma spp.*, and rarely with *M. hominis*, in preterm infants has been associated with higher incidence of pneumonia, severe respiratory failure, bronchopulmonary dysplasia, and ultimately with death [Viscardi et al., 2002]. These bacteria can be transmitted from infected females to their fetus or newborn by three main different routes: a) Ascending intrauterine infection from vaginal colonization; b) Hematogenous spreading from placental infection, and c) Acquisition of the microorganism

by the neonate during passage through an infected maternal birth canal. [Viscardi et al., 2002; Waites et al., 2005]. An inverse correlation between ureaplasma vertical transmission rate and gestational age has been established, and this increases with duration of premature rupture of membranes. Improved molecular detection of colonizing *Ureaplasma* in respiratory tract specimens suggests a higher frequency of colonization in very low birth weight infants than that previously reported with culture-based studies (25–48% vs. 20%) [Viscardi & Hasday, 2009].

Infrequently, *M. fermentans* has been detected in adults who developed respiratory distress syndrome and/or from bronchoalveolar lavage in AIDS patients with pneumonia, highlighting the potential of this species to cause lower respiratory tract disease in susceptible hosts [Waites & Talkington, 2004].

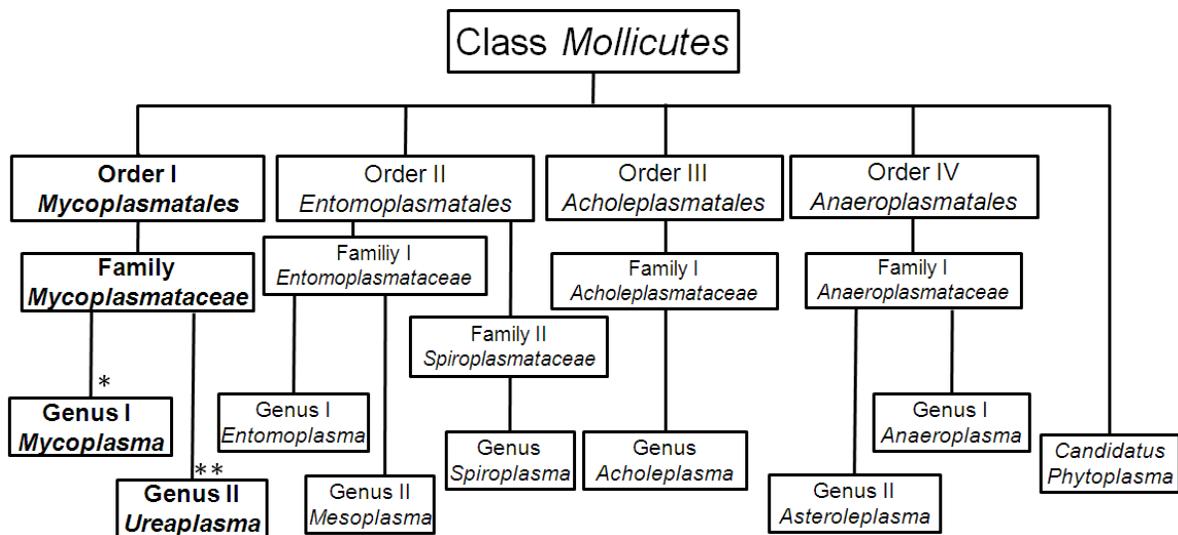
2. Taxonomic characterization of Mollicutes

Modern mycoplasmal taxonomy relies on combined data from phenotypic traits and phylogeny based on the 16S rRNA gene sequences [Brown et al., 2007; International Committee on Systematics of Prokaryotes- Subcommittee on the taxonomy of Mollicutes (ICSP-STM), 2010]. Among the phenotypic characteristics, there are few useful metabolic markers including the ability to ferment glucose, the ability to hydrolyze urea and arginine, and dependence on cholesterol for growth and anaerobiosis. Despite the high rate of surface antigenic variation, serologic relatedness at the species level is still used in routine identification of mycoplasmas [Brown et al., 2007; ICSP-STM, 2010; Razin et al., 1998]. There are currently more than 200 species allocated into four orders, five families and eight genera within the class *Mollicutes* (Figure 1), including the undefined *candidatus Phytoplasma* [Brown et al., 2007; ICSP-STM, 2010].

2.1 Phylogeny, genome content and molecular analysis

The Mollicutes 16S rRNA-based phylogenetic tree is monophyletic arising from a single branch of the *Clostridium ramosum* branch. The Mollicutes split into two major branches: the AAP branch, containing the *Acholeplasma*, *Anaeroplasm*a and *Asteroleplasma* genera, and the *Candidatus Phytoplasma* phyla; the other is the SEM branch that includes the *Spiroplasma*, *Entomoplasma*, *Mesoplasma*, *Ureaplasma* and *Mycoplasma* genera [Johansson et al., 1998; Maniloff 1992; Razin et al., 1998]. Interestingly, the genus *Mycoplasma* is polyphyletic, with species clustering within the *Spiroplasma*, *Pneumoniae* and *Hominis* phylogenetic groups [Behbahani et al., 1993; Johansson et al., 1998; Maniloff 1992]. Nevertheless, additional phylogenetic markers such as the elongation factor EF-Tu (*tuf*) gene, ribosomal protein genes, the 16S/23S rRNA intergenic sequences, etc, have been already used as complementary comparative data, thus there is no unique phylogenetic tree for *Mollicutes* [Razin et al., 1998].

The mycoplasmas may have evolved through regressive evolution from closely related Gram positive bacteria with low content of guanine plus cytosine (G+C), probably the Clostridia or *Erysipelothrix* [Bove, 1993; Brown et al., 2007; Razin et al., 1998]. The massive gene losses (i.e. genes involved in cell wall and amino acid biosynthesis) had left mycoplasmas with a coding repertoire of 500 to 2000 genes [Sirand-Pugnet et al., 2007]. The G+C content in DNA of mycoplasmas varies from 23 to 40 mol%, while genome size range is 580–2200 Kbp, much smaller than those of most walled bacteria [Razin et al., 1998].



* Includes more than one hundred species. At present five species are recognized human pathogens.

** Includes seven species, two of them are pathogenic for humans.

Adapted from: Razin et al, 1998.

Fig. 1. Taxonomy of Class Mollicutes.

From a comparative analysis of the complete genome sequences from 17 mycoplasma species, Sirand-Pugnet et al., 2007, identified 729 clusters of orthologous groups of proteins (COGs) that represent 21 categories of diverse cellular functions. This analysis revealed that mycoplasmas shared a limited core genome (i.e. the essential translation machinery), while there is a wide diversity of COGs that are only found in one or a few species. Moreover, frequent chromosomal rearrangements occurring at specific loci involved in expression of surface proteins were also identified [Momynaliev & Govorun, 2001; Sirand-Pugnet et al., 2007].

3. Immune response

Host defense in respiratory mycoplasmosis is dependent on both innate and humoral immunity. In general terms, mycoplasmas reaching the lower respiratory tract may be opsonized by antibody and complement, and then activated macrophages begin phagocytosis and migration to the site of infection by chemotaxis. Finally, complement-mediated cytolysis may then play a role in limiting the growth of the mycoplasmas. However, immunity against mycoplasmal infection is typically short-lived, hence infection recurrence is common (Waites et al., 2007, 2008).

3.1 Innate and adaptive immune response

M. pneumoniae infection is able to activate the host innate immune system, so the inflammatory event elicited by accounts for the early signs and symptoms of the infection. After become opsonized, *M. pneumoniae* is susceptible to complement-mediated cytolysis, probably through both the alternative and classical pathways [Waites et al., 2007]. It has been suggested that innate immune recognition of *M. pneumoniae* has also a pivotal role for mucin expression in the airway, at both mRNA and protein levels, since blockage of the toll-like receptor (TLR)-2 signaling pathway results in marked reduction of mucin expression [Chu et al., 2005]. Moreover, *M. pneumoniae* is capable of interact with mast cells and surfactant protein (SP)-A, resulting in cytokine production and bacterial growth inhibition, respectively [Waites et al, 2007].

After primary encounter with *M. pneumoniae*, the immune system of an immunocompetent host responds by rapidly producing antibodies (mainly directed against the P1 adhesin and glycolipid antigens) that peak after 3 to 6 weeks, followed by a gradual decline over months to years [Waites & Talkington, 2004]. The onset of symptoms may coincide with demonstrable antibody titers due to prolonged incubation period. Acute infection can often be difficult observed by evidence of rising *M. pneumoniae*-specific IgM antibodies, especially in pediatric populations. [Waites, 2007, 2008]. IgA antibodies are produced early in the course of disease, rise quickly to peak levels, and decrease earlier than IgM or IgG [Waites & Talkington, 2004]. Adaptive immunity, characterized by both B and T lymphocyte responses, has a major impact on the progression of *M. pneumoniae* respiratory disease. Mycoplasmas activate the immune system by inducing non-specific proliferation of B- and T-lymphocyte populations (mitogenic stimulation), thereby inducing autoimmune responses with concurrent production of cytokines (Table 2). Immune responses that develop after infection often fail

Organism	Cells / Experimental system	Cytokine(s) released
<i>M. pneumoniae</i>	<ul style="list-style-type: none"> Lung Alveolar type II pneumocytes Nasal epithelial cells/peripheral blood macrophages Peripheral blood mononuclear cells Lung epithelial carcinoma A549 cells <i>M. pneumoniae</i>-infected patients 	<p>Interleukin (IL)-1β, tumour necrosis factor (TNF)-α, IL-8.</p> <p>IL-2, IL-6, RANTES, intercellular adhesion molecule (ICAM)-1, transforming growth factor (TGF)-β1 and TNF-α</p> <p>IL-1β, IL-2/IL-2R, IL-6, Interferon (IF)-γ, and TNF-α.</p> <p>IL-1β, IL-8, and TNF-α.</p> <p>IL-2/IL-2R, IL-4, IL-5, IL-6, IL-8, IL-12, IL-18, IF-γ, and TNF-α.</p>
<i>Ureaplasma</i> spp.	<ul style="list-style-type: none"> Neonatal fibroblasts Peripheral blood/Cord blood monocytes THP-1-derived macrophages / Human lung fibroblasts THP-1 monocytes 	<p>IL-6 and IL-8.</p> <p>TNF-α, IL-8, IL-6, and IL-10.</p> <p>TNF-α, IL-6, ICAM-1, and vascular endothelial growth factor (VEGF).</p> <p>IL-1α, TNF-α, and IL-8.</p>

Data from Dakhama et al., 2003; Kazachkov et al., 2002; Li et al., 2000a; Manimtim et al., 2001; Peltier et al., 2008 ; Stancombe et al., 1993; Yang et al, 2004.

Table 2. Mycoplasma-induced cytokine secretion.

to eliminate the mycoplasma, indicating that adaptive immunity apparently has a limited effect on clearance of an established infection, thus leading to asymptomatic carriage for variable periods of time. Cytokine production and lymphocyte activation may either minimize disease through the enhancement of host defense mechanisms and subsequent elimination of the infecting organisms, or exacerbate disease through the development of immunologic hypersensitivity [Waites et al, 2007, 2008]. It has been suggested that there is no correlation between severity of pneumonia caused by *M. pneumoniae* and T-cell deficiencies, thus cell-mediated defense against respiratory mycoplasmosis appears to be rather limited [Cartner et al, 1998].

Molecular mimicry, survival within cells and phenotypic plasticity (antigenic variation) are the major mechanisms by which mycoplasmas evade the immune response [Chambaud et al, 1999; Razin et al., 1998; Rottem & Naot, 1998]. Furthermore, a transient impairment of T-lymphocyte function, or depletion of CD4+ T cells, can be induced by *M. pneumoniae* [Waites et al., 2007].

In the context of perinatal pneumonia, very low birth weight infants have relative deficiencies in mucosal barrier function and in both the innate and adaptive immune responses. These immature hosts may generate poor immune responses, including secretory IgA, serum complement components, defensins, fibronectin, and altered cytokine production. Impaired chemotaxis, phagocytosis, and microbial killing by neonatal immune cells highlight the vulnerability of preterm neonates to systemic infections, and partially explain the eventual systemic spread of bacteria [Waites et al., 2005].

3.2 Cell culture models

Mycoplasmas possess an impressive capability of maintaining a dynamic surface architecture that is antigenically and functionally versatile, contributing to their capability to adapt to a large range of habitats and cause diseases that are often chronic in nature [Rottem, 2003]. The probable role of mycoplasmas in chronic respiratory diseases has been studied *in vitro* using diverse cell culture models. Several of these models are focusing in the study of adherence, invasion and fusion as the strategies to induce damage to the host cells [Baseman et al., 1995; Razin, 1999; Rottem, 2003].

M. pneumoniae is the most extensively studied system with respect to adhesions and receptors [Rottem, 2003] because of its significance as pathogen for humans. Models in human lung cells analyzed by immunofluorescence and confocal microscopy reveal that *M. pneumoniae* parasitize cells surface, enter the intracellular spaces and locate throughout the cytoplasmic and perinuclear regions within 2 hr postinfection [Baseman et al., 1995]. The microorganism can survive within the host cells for prolonged periods of time, well protected from the immune system and from de action of many antibiotics and may explain its pathogenic potential [Yavlovich et al., 2004]. Another *in vitro* studies show that this microorganism has a polar, tapered cell extension at one of the poles containing an electron-dense core in the cytoplasm. This structure, termed the tip organelle, functions both as an attachment organelle and as the leading end in gliding motility [Baseman et al., 1995; Razin, 1999; Rottem, 2003; Svenstrup et al., 2002]. Host-pathogen studies in an air-liquid culture of differentiated human airway epithelial cells revealed that the microorganism bounds initially to ciliated epithelial cells, but colonization become more evenly distributed over the entire surface with time [Krunkosky et al., 2007]. We recently studied the adherence of *U. urealyticum* to a respiratory epithelial cell line, as a virulence factor for lung disease. We

describe that *U. urealyticum* induce changes in cell morphology mediated probably by the loss of microvilli, and that the microorganism invades the cell forming vacuoles [Torres-Morquecho et al., 2010].

Since chronic lung disease is characterized by an early increased number of activated neutrophils and alveolar macrophages, with later architectural epithelial and endothelial cell damage [Li et al., 2002], all of these cells represent excellent targets for the study of mycoplasmal infections. As the key processes occurring in all respiratory diseases are the exacerbation of lung inflammation and injury, most of the *in vitro* models have been developed to study the inflammatory response mediated primarily by cytokines.

Different studies have demonstrated that the release of Interleukin (IL)-2, IL-6 RANTES, ICAM-1, TGF- β 1 and TNF- α by human nasal epithelial cells and peripheral monocytes infected with *M. pneumoniae* could be implicated in the asthma exacerbation in children and may play a role in the pathogenesis of chronic asthma [Dakhama et al., 2003; Kazachkov et al., 2002; Krunkosky et al., 2007]. Additionally, it has been recently demonstrated that *M. pneumoniae* infection induces reactive oxygen species and DNA damage in human lung cells [Sun et al., 2008].

A number of studies show that *Ureaplasma urealyticum* induce the production of TNF- α , IL-8, IL-6 [Li et al., 2000a; Manimtim et al., 2001; Peltier et al., 2008], NF- κ B and nitric oxide [Li et al., 2000b] by human macrophages and monocytes. Infection assays in macrophages performed in combination with LPS showed that *U. urealyticum* enhances the proinflammatory response to a second infection by blocking expression of counterregulatory cytokines (IL-6 and IL-10), predisposing the preterm infant to prolonged and dysregulated inflammation, lung injury, and impaired clearance of secondary infections [Manimtim et al., 2001]. Furthermore, *U. urealyticum* stimulates macrophages to produce vascular endothelial growth factor (VEGF) and intercellular adhesion molecule-1 (ICAM-1) *in vitro*, which are potentially associated with both early and later pathological changes in the lung during the development of chronic lung disease [Li et al., 2002a]. The same raise in proinflammatory cytokine release is observed when *U. urealyticum* interacts with neonatal pulmonary fibroblast [Stancombe et al., 1993], suggesting a role in the development of bronchopulmonary dysplasia. Finally, it has been demonstrated that *U. urealyticum* induces apoptosis in human lung epithelial cells and macrophages [Li et al., 2002b], involving in impairing lung structure observed in chronic lung disease.

4. Lung disease in humans

4.1 *Mycoplasma pneumoniae*

Respiratory infections due to *M. pneumoniae* can affect either the upper or the lower tract, or both simultaneously. This pathogen is responsible for up to 40% of cases of community-acquired pneumonia [Atkinson, et al., 2008]. Nearly 50% of the *M. pneumoniae*-infected patients show non-specific signs and symptoms, often similar to those produced by other respiratory pathogens such as *Chlamydophila pneumoniae*, *Streptococcus pneumoniae* and some viruses, and although these infections are usually mild or asymptomatic, they are not always self-limiting [Waites & Talkington, 2004; Waites et al., 2008].

Symptomatic disease emerges gradually within few days post-infection and persists for several weeks or months. Upper respiratory tract symptoms include sore throat, fever, cough, headache, coryza, myalgias, chills, earache and malaise. Clinical manifestations of lower respiratory tract infections generally include: non-productive cough which later turns

productive with non-hemorrhagic sputum, dyspnoea, adenopathy, wheezing and, rarely, respiratory failure [Waites & Talkington, 2004; Waites et al., 2008].

4.1.1 Pathogenesis

Occurrence of airway disease initiates from the close interplay between the microorganism and the mucosal epithelium as a result of cytoadherence, the main virulence factor of the bacterium, which is mediated through a polarized tip attachment organelle. This tip structure comprises the main protein adhesin, named P1, along with several other adhesins and accessory proteins (High Molecular Weight [HMW]-1, HMW-2, HMW-3, Protein [P]-90, P-40 and P-30) [Waites et al., 2008].

Unlike other bacterial lung pathogens (*S. pneumoniae*, *Pseudomonas aeruginosa* and *Haemophilus influenzae*) which bind specifically to glycolipids containing unsubstituted GalNAc β 1-4Gal residues, *M. pneumoniae* attaches to host cells either through a sialic acid-free glycoprotein or sulfated glycolipids containing terminal Gal(3SO₄)₁ residues. It is worthy to note that the apical microvillar border and cilia of the epithelium express the sialoglycoconjugate-type receptors, thus allowing the selective attachment of *M. pneumoniae* to the ciliated cells [Krivan et al., 1988, 1989; Roberts, D.D. et al, 1989; Olson & Gilbert, 1993; Rottem & Naot, 1998].

Cytoadhered *M. pneumoniae* is able to cause damage through generation of reactive oxygen species (ROS), which act in concert with host's endogenous ROS to induce oxidative stress. Bacteria-derived superoxide anions act to inhibit catalase in host cells, thereby reducing the enzymatic breakdown of peroxides, rendering the host cell more susceptible to oxidative damage [Rottem & Naot, 1998; Waites et al., 2004]. Mycoplasmal species exert primarily deleterious effects on the host respiratory epithelium, such as ciliostasis and apoptosis, resulting in localized damage and an immune response which, although often robust, is poorly efficacious in terms of clearing the organism or preventing subsequent reinfections [Waites et al., 2004].

Recently, a *M. pneumoniae* protein homolog to the pertussis toxin S1 subunit was identified and it showed specific binding to surfactant protein A [Kannan et al., 2005] This protein also showed protein:ADPribosyltransferase activity, inducing vacuolation and ciliostasis in cultured host cells. This immunodominant protein has been named as community-acquired respiratory distress syndrome toxin (CARDS TX). Host-cell targets for CARDS TX remain unidentified at present, as does how the toxin's function might relate to its specific binding to surfactant protein A [Kannann & Baseman, 2006; Waites et al., 2004, 2008].

Cytopathic effects observed in *M. pneumoniae*-infected host cells include loss of ciliated epithelia, cell vacuolation, reduced oxygen consumption, reduced glucose utilization, diminished amino acid uptake and macromolecular synthesis, ultimately leading to exfoliation. Clinically, the above mentioned events in the lung tissues are noticeable by the persistent hacking cough [Waites et al., 2004, 2008].

Some clinical characteristics of *M. pneumoniae* infections are consistent with an intracellular location of the pathogen, mainly the establishment of latent or chronic infections, limited efficacy of some antimicrobials, necessity for prolonged treatment to eradicate infection in some instances and circumvention of the host immune response [Waites & Talkington, 2004]

4.1.2 Role in COPD and asthma

Chronic obstructive pulmonary disease (COPD) is an inflammatory disorder of the lungs that leads to blockage of the airways which eventually interferes with the exchange of

oxygen and carbon dioxide, making breathing progressively more difficult. It is mainly associated with long-term smoking, but presence of persistent bacterial infections has been related to the etiology, pathogenesis and clinical course of COPD [Blasi, 2004; Sethi, 2000].

Well-known bacterial pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* have been associated with acute exacerbations in COPD and asthma. [Guilbert & Denlinger, 2010; Sethi, 2000; Waites & Talkington, 2004]. Since late 1970's, several authors suggested a relationship between COPD and *M. pneumoniae* infection [Buscho *et al.*, 1978; Gump *et al.*, 1976; Smith *et al.*, 1980], but it was until late 1990's and early 2000's that several studies based on serology brought attention once more on this issue. [Lieberman *et al.*, 2001, 2002; Mogulkoc *et al.*, 1999]. It is well known that mycoplasmas species pathogenic for humans have the ability to induce chronic disease states in which clearance of the bacteria is extremely difficult. [Rottem & Naot, 1998].

A growing body of evidence indicates that there is a link between *M. pneumoniae* infection and COPD. In a Yemeni study, *M. pneumoniae* infection was demonstrated by culture and serologic methods in 20.4% (11/54) of COPD patients [Al-Moyed & Al-Shamahy, 2003]. In a group of 144 Dutch patients with CAP, 12.5 % were infected with *M. pneumoniae* and less than 40% of these *M. pneumoniae*-infected patients had COPD, even though specific serologic tests were mainly negative [Dorigo-Zetsma *et al.*, 2001]. In contrast, *M. pneumoniae* was the most frequent pathogen (22.7%, alone or in association with other microorganisms) among CAP patients that required hospitalization related to COPD, asthma and/or pulmonary fibrosis. [Caberlotto *et al.*, 2003].

A rather weak association between *M. pneumoniae* infection and acute asthma has been suggested on the basis of contradictory data about mycoplasma infection frequencies from several trials. Conversely, strong associations of this pathogen with chronic asthma have been established [Guilbert & Denlinger, 2010; Sutherland & Martin, 2007]. Evidence for this association includes the following: a) Higher prevalence of *M. pneumoniae* in asthmatics than in healthy subjects; b) Improved pulmonary function in mycoplasma-infected asthmatic patients after treatment with macrolide antibiotics; c) Demonstration of long-term airway dysfunction consistent with a persistent infection; and d) *M. pneumoniae*-induced production of inflammatory mediators (IgE, substance P and neurokinin 1, and IL-5) implicated in the pathogenesis of asthma [Waites & Talkington, 2004].

By means of murine models of chronic respiratory infection, it has been demonstrated *M. pneumoniae* can produce pneumonia, with consistent immunologic responses in term of specific IgM antibodies [Wubbel *et al.*, 1998]. Other findings revealed post-infection time-dependent differential cytokine production, with increased expression of TNF- α , IL-1, IL-6, and IFN- γ in the acute phase, whereas IL-2 and IL-2 receptor gene expression was seen only during reinfection. [Pietsch *et al.*, 1994].

Relationship between the timing of Mycoplasma infection, allergic sensitization, and subsequent pulmonary physiologic and immune response was assessed by Chu *et al.*, 2003. Before ovalbumin sensitization, experimental *M. pneumoniae* infection resulted in reduced airway hyperresponsiveness (AHR), reduced lung inflammatory cell recruitment, and a predominantly Th1 response. In contrast, *M. pneumoniae* infection post-sensitization initially caused a transient reduction in AHR, followed by augmented AHR, and a Th2-dominant airway inflammatory process that potentiates organism survival in the lungs. Further characterization of the *M. pneumoniae* effects on ovalbumin sensitized mice, long-term infection provoked collagen deposition in airway wall accompanied by augmented expression of TGF- β 1 in the lungs [Chu *et al.*, 2005].

4.2 *Mycoplasmas* in immunocompromised hosts

Association between immunodeficiency and mycoplasmal infections has been reported since the mid 1970s to the date. Mycoplasmas can disseminate from localized infections and cause invasive diseases, especially in hypogammaglobulinemic subjects. Significance of mycoplasma species other than *M. pneumoniae* or *Ureaplasma* spp. in respiratory diseases is a matter of controversy [Cassell et al., 1994a].

4.2.1 *Mycoplasma fermentans* associated to lung diseases

It has been well documented that *M. pneumoniae* produces respiratory disease in adults; it 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 [Waites et al., 2005]. However, 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*, *M. genitalium*, and *M. penetrans* in humans. Waites and Talkington, 2005, recently reviewed the importance of *M. fermentans* in human diseases and provided more detail on the conditions described above as well as others [Waites et al., 2005].

The role of *M. fermentans* as a pathogen is unclear, it has been associated with the pathogenesis of rheumatoid arthritis [Williams et al., 1970]. However, the potential importance of *M. fermentans* in human diseases has recently been further demonstrated. Isolation of about 30 strains of *M. fermentans* from previously healthy non-AIDS patients who had a sudden onset of a severe and often fatal form of respiratory distress syndrome was recorded by R. Dular in Ottawa, Canada [unpublished, as cited by Hu et al., 1998]. Also they have reported the detection by PCR of *Mycoplasma fermentans* in the respiratory tract of children with pneumonia [Cassell et al., 1994b]. It has been demonstrated that a wild strain of *M. fermentans* isolated from the respiratory tract of an asthma patient was able to produce severe experimental respiratory disease in hamsters [Yáñez, 1997]. Román-Méndez et al., 2007, have showed that *Mycoplasma fermentans* persisted in the respiratory tract of hamsters during 120 days and all hamsters developed histological evidence of pulmonary inflammation. Lo et al., 1993, have reported the presence of infections due to *Mycoplasma fermentans* in patients with adult respiratory distress syndrome with or without systemic disease. *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 [Ainsworth et al., 2000a, 2001; Gilroy et al., 2001; Lo et al., 1989; Schaeffer et al., 1996; Taylor-Robinson, 1996; Tully, 1993; Waites & Talkington, 2005]

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. [Taylor-Robinson, 1996].

M. fermentans has also been detected in adults with an acute influenza-like illness who developed respiratory distress syndrome, 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 [Lo et al., 1993; Ainsworth et al., 2001]. This mycoplasma is also known to colonize mucosal surfaces in healthy persons, complicating efforts to understand its role in disease [Ainsworth et al., 2000b].

Mycoplasma fermentans, isolated decades ago from the urogenital tract, has been implicated in several disease conditions. Interest in this organism has recently increased because of its

possible role in the pathogenesis of rheumatoid arthritis. Over the last decade, intensive studies have been carried out in order to understand the strategy employed by *M. fermentans* to interact with host cells and to avoid or subvert host protective measures [Rechnitzer et al., 2011].

Attention was focused on *M. fermentans* in the late 1980's because of reports that it may be important as a mediator or cofactor in the development of AIDS [Lo et al., 1989; Saillard et al., 1990]. The identification of mycoplasmal membrane components that participate in the adhesion of the parasite and the finding that some mycoplasmas can reside intracellularly [Rottem, 2003] open up new horizons in the study of the role of mycoplasma and host surface molecules in mycoplasma-host cell interactions [Rechnitzer et al., 2011].

Unlike *M. pneumoniae*, *M. fermentans* lacks a well-defined terminal attachment tip to mediate attachment and cell invasion. Since intracellular organisms are resistant to host defense mechanisms and to antibiotic treatment, this feature may account for the difficulty in eradicating mycoplasmas from cell cultures. A study by Yavlovich et al., 2001, demonstrated that *M. fermentans* binds plasminogen and converts it to plasmin, where upon 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, cytoadherence, and antigenic variation, are discussed by Rottem, 2003. The fusion of *M. fermentans* with eukaryotic host cells raises exciting questions on how microinjection of mycoplasmal components into eukaryotic cells affects host cells [Rottem, 2003].

The fusion process as well as the invasion of host cells by *M. fermentans* brings up an emerging theme in mycoplasma research, the subversion by *M. fermentans* of host cell functions mainly in signal-transduction pathways and cytoskeletal organization [As cited by Rechnitzer et al., 2011].

4.2.2 *Mycoplasma penetrans*, *Mycoplasma pirium* and Human Immunodeficiency Virus (HIV) disease

M. penetrans was first isolated from urine of homosexual men infected with (HIV), but not from healthy age-matched subjects. Subsequent studies suggested an association of this mycoplasma with Kaposi's sarcoma, but later findings did not confirm such association. This organism has been detected in HIV-negative persons, and despite its ability to invade epithelial cell, there is no conclusive evidence of any significant role in human disease [Yañez et al., 1999; Waites et al, 2005; Baseman & Tully, 1997].

Initial isolation of *M. pirium* from human peripheral blood lymphoid cells of HIV-positive patients, along with *M. penetrans* and *M. fermentans*, lead scientists to suggest a role as cofactor in acquire immunodeficiency syndrome (AIDS) progression. However, despite *M. pirium* was detected in rectal specimens of homosexual men and in urine of patients with AIDS, no conclusive evidence of its pathogenic role in human disease has been found. [Waites et al, 2005; Baseman & Tully, 1997]. Taking into account that *M. penetrans* and *M. pirium* have been associated with immune compromise, extragenital dissemination in infected patients, including respiratory disease, should be considered.

4.3 *Ureaplasma urealyticum* and *Ureaplasma parvum* in urogenital and respiratory tract infections

Although *U. urealyticum* and *U. parvum* are common commensals of the urogenital tract of humans, they are considered as important pathogens associated with infertility and non-

gonococcal urethritis in men, multiple obstetrical complications in women, and neonatal lung disease [Viscardi, 2010; Volgmann et al., 2005; Waites et al., 2005].

Genital ureaplasmas are natural residents of male urethra contaminating the semen during ejaculation. However, these microorganisms, particularly *U. urealyticum*, play an etiologic role in both genital infections and male infertility (Gdoura et al., 2008). Recent studies reveal that *U. urealyticum* strains are isolated more often in men with non-gonococcal urethritis than in healthy men (Deguchi et al., 2004; Maeda et al., 2004; Povlsen et al., 2002). Ureaplasmas are widespread among the male partners of infertile couples (Gdoura et al., 2007, 2008), and their presence is correlated with the alteration of some characteristics of semen, such as density, sperm motility, concentration, and probably morphology (Naessens et al., 1986; Reichart et al., 2000; Wang et al., 2006). The attachment to sperm and the induction of germ cell apoptosis have been proposed as mechanisms by which *U. urealyticum* affects sperm quality (Shang et al., 1999; Waites et al., 2005).

The infection of the female urinary tract with *U. urealyticum* is frequently overlooked. However, since a high isolation rate of this microorganism has been observed in urine and urethral samples from women with unexplained chronic urinary symptoms, treatment of the infection is now indicated (Baka et al., 2009; Potts et al., 2000).

Genital ureaplasmas can be found in vaginal flora in 40% of sexually inactive and 67% sexually active women (Viscardi, 2010). The infection is generally asymptomatic in nature, and is sexually transmitted between partners. Ureaplasmas can survive in the reproductive tract for many years, undetected, until the patient is specifically tested for the infection.

U. urealyticum is recovered from the lower genital tract of 70-80% of pregnant women (Carey et al., 1991; Volgmann, 2005), but vaginal carriage is not reliably predictive of preterm birth (Kafetzis et al., 2004; Povlsen et al., 2001). However, there is a consistent association when the infection is present in the amniotic fluid, chorioamnion or placenta (Eschenbach, 1993; Kundsin et al., 1996; Yoon et al., 2000, 2003). The secretion of phospholipases A and C has been suggested to be the means by which ureaplasmas may initiate preterm labor by liberating arachidonic acid and altering prostaglandin synthesis (De Silva & Quinn, 1986). In addition, recently we reported that the interaction between *U. urealyticum*, intrauterine leukocytes and fetal membranes results in the secretion of high amounts of IL-1b and prostaglandin E2, which could induce uterine contraction leading to preterm labor (Estrada et al., 2010). Isolation of *U. urealyticum* from chorioamnion has been consistently associated with histological chorioamnionitis and is inversely related to birth weight, even when adjusting for duration of labor, rupture of the fetal membranes, and the presence of other bacteria [Cassel et al., 1993; Waites et al., 2005].

There is accumulating epidemiologic and experimental evidence that intrauterine or postnatal infection with genital ureaplasmas is a significant risk factor for complications of extreme preterm birth such as bronchopulmonary dysplasia (BDP) and intraventricular hemorrhage [Kafetzis, et al., 2004; Viscardi, 2010]. *Ureaplasma* spp can be transmitted from an infected mother to the fetus or neonate by ascending intrauterine infection, hematogenous route involving umbilical vessels, or through passage of an infected maternal birth canal with resultant colonization of the skin, mucosal membranes or respiratory tract [Waites, 2005].

Among premature infants, respiratory tract colonization with genital ureaplasmas has been associated with pneumonia, chronic lung disease, infant wheezing, respiratory distress syndrome, acute respiratory insufficiency, and increased mortality [Cultrera et al., 2006;

Kafetzis et al., 2004]. For some infants, ureaplasma infection triggers a vigorous response in the lungs involving the elevation of adhesion molecules, collagenases, proinflammatory cytokines and neutrophil activation and migration, which increase the risk of developing bronchopulmonary dysplasia characterized by delayed alveolarization, chronic inflammation, and fibrosis [Manimtim et al., 2001; Schelonka & Waites, 2007]. Additionally, free radical generation and oxidative injury induced by recruited neutrophils could contribute to lung damage [Buss et al., 2003]. Apoptosis of pneumocytes and pulmonary mesenchymal cells has been shown to occur as part of the pathogenesis of *U. urealyticum* [Li et al., 2002], while *U. parvum* lipoproteins activate NF- κ B and induce TNF- α in macrophages, favoring the inflammatory response (Shimizu et al., 2008). Apparently, there is no trend in the prevalence of either species between infants with or without bronchopulmonary dysplasia [Katz et al., 2005].

5. Diagnostic procedures

Much of the mycoplasmal respiratory diseases, especially those caused by *M. pneumoniae*, are underdiagnosed because the laboratory diagnostic strategies are quite different than those for fast-growing bacteria. It is noteworthy that mycoplasmal etiology of respiratory diseases is considered only after failure of diagnosis of other common bacterial etiologies. In addition, there are few specialized or reference laboratories and skilled personnel [Cassell et al., 1994a; Waites et al., 2000].

5.1 Types of specimens, transport and collection

Detection or isolation of mycoplasmas in clinical specimens requires careful consideration of the type of specimen available and the organism (species) sought [Cassell et al., 1994a]. Specimens appropriate for laboratory diagnosis of respiratory mycoplasmal infections include: Bronchoalveolar lavage (BAL), sputum, pleural fluid, nasopharyngeal and throat swabs, endotracheal aspirates (ETA) and lung biopsies. Liquid specimens or tissues do not require special transport media if culture can be performed within 1 hour, otherwise specimens should be placed in transport media, such as SP-4 broth, 10B broth or 2SP broth. When swabbing is required, aluminum- or plastic-shafted calcium alginate or dacron swabs should be used, taking care to obtain as many cells as possible [Atkinson et al., 2008; Cassell et al., 1994a; Waites et al., 2002].

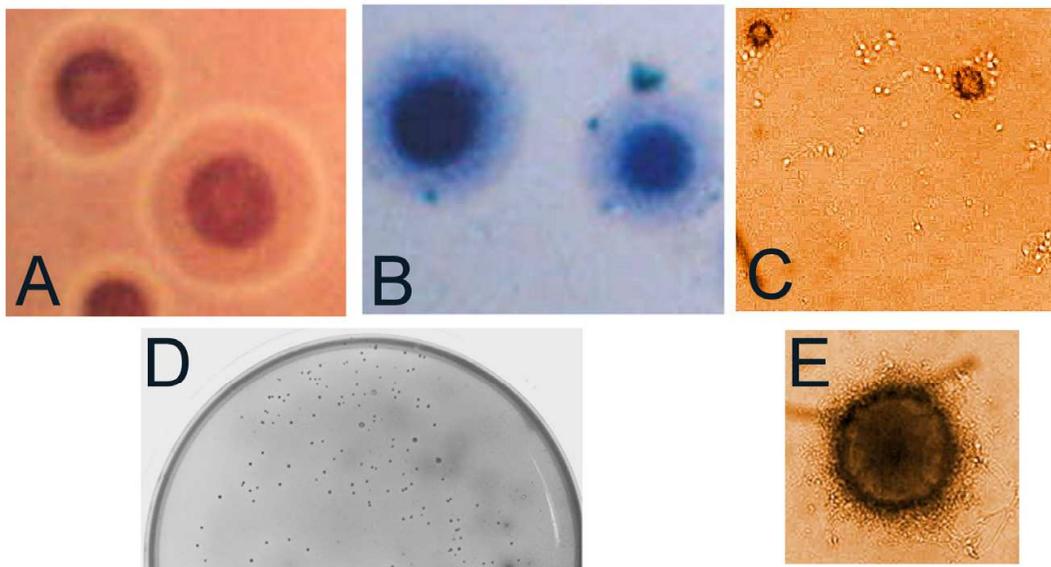
Other specimens such as blood, cerebrospinal fluid, pericardial fluid and synovial fluid must be considered when extrapulmonary disease is suspected, thus specimen collection should reflect the site of infection and/or the disease process. [Atkinson et al., 2008; Waites & Talkington, 2004].

5.2 Culture

Routine culture methods for isolation/detection of most mycoplasma species are time-consuming, thus emission of results may delay up to 5-6 weeks. Furthermore, there is no ideal formulation of culture media for all pathogenic species, mainly due to their different substrate and pH requirements [Waites et al., 2000]. Modified SP-4 media (broth and agar) [Lo et al., 1993], containing both glucose and arginine, can support the growth of all human pathogenic *Mycoplasma* species, including the fastidious *M. pneumoniae* and *M. genitalium*. A set of Shepard's 10B broth and A8 agar can be used for cultivation of *Ureaplasma* species and *M. hominis*.

For cultivation, specimens in transport media should be thoroughly mixed, and then should be 10-fold serially diluted in broth (usually up to 10^{-6}) in order to overcome potential inhibitory substances, and to allow semiquantitative estimation of mycoplasmal load. Subcultures in agar media should be also performed. [Cassell et al., 1994a]. All inoculated media are incubated under microaerophilic atmosphere at 37°C.

Detection of *M. pneumoniae* in broth culture is based on its ability to ferment glucose, causing an acidic shift after 4 or more days, readily visualized by the presence of the phenol red pH indicator. Broths with any color change, and subsequent blind broth passages, should be subcultured to SP4 agar, incubated, and examined under the low-power objective of the light microscope in order to look for development of typical “fried egg”-like colonies of up to 100 μm in diameter (Figure 2). Examination of agar plates must be done on a daily basis during the first week, and thereafter every 3 to 4 days until completing 5 weeks or until growth is observed [Waites et al., 2000, 2004]. *M. genitalium*, *M. fermentans* and *M. penetrans* are also glucose-fermenting and formed colonies morphologically indistinguishable from those of *M. pneumoniae*, thus serologic-based definitive identification can be done by growth inhibition, metabolic inhibition, and mycoplamacidal tests [Cassel et al., 1993].



A) Typical “Fried-egg” appearance of *Mycoplasma* spp. colonies on SP-4 agar. B) Dienes-stained mycoplasma colonies. C) Tiny brown-colored ureaplasma colonies on modified SP-4 agar. D) Macroscopic view of Dienes-stained mycoplasma colonies growth on SP-4 agar in 30 mm-diameter Petri dishes. E) Closer view of an ureaplasma colony.

Fig. 2. Morphology of mycoplasma colonies in culture.

Hidrolisis of urea by *Ureaplasma* and hidrolisis of arginine by *M. hominis* cause an alkaline shift, turning the colour of 10B broth from yellow to pink. Tiny brown or black irregular colonies of *Ureaplasma* species develop between 1 -5 days on A8 agar plates, due to urease production in the presence of manganese sulfate (Figure 2). Typical fried egg colonies are produced by *M. hominis* in this medium [Cassell et al., 1994a, Waites et al., 2000].

5.3 Immunodiagnosis by serological tests

As culture of *M. pneumoniae* is slow and insensitive, the laboratory diagnosis of *M. pneumoniae* infection has largely relied on serological testing. Seroconversion or rising

specific antibody titers are observed among *M. pneumoniae*-infected patients. This immunologic response can be measured by several tests, including: metabolic inhibition assay, complement fixation or enzyme-linked immunoassays (EIA). Serum samples are easy to collect and handle, but it is required paired acute- and convalescent-phase specimens. Commercial assay formats include indirect immunofluorescence, particle agglutination assay, and EIA [Atkinson et al., 2008, Cassell et al., 1994a; Waites & Talkington, 2004].

Prior to the widespread availability of commercialized antibody assays, presence of cold agglutinins (IgM antibodies that are produced 1 to 2 weeks after initial infection in about half of *M. pneumoniae*-infected subjects) was used to confirm primary atypical pneumonia (Waites & Talkington, 2004). Although there have been recent improvements, the sensitivity and specificity of antibody detection is still suboptimal. Nevertheless, the complex and time-consuming nature of many of the serological assays that have been used in the past have limited acceptance of serology for routine diagnostic testing. [Cassell et al., 1994a; Waites et al., 2000].

At present, besides research laboratories, no serologic tests assays for mycoplasmas other than *M. pneumoniae* have been standardized for diagnostic purposes in routine clinical microbiology laboratories nor made commercially available elsewhere. [Cassell et al., 1994a, Waites et al., 2005].

5.4 PCR and other molecular tests

Nucleic acid amplification techniques (NAATs) are more sensitive, and considerably more rapid than culture, showing a fair to good correlation with serology. PCR testing for species-specific mycoplasmal infection are suitable for both upper and lower respiratory samples. Interestingly, sample processing prior amplification must be optimized depending of the type of specimen to overcome the presence of PCR inhibitors (i.e., nasopharyngeal samples have higher rate of PCR inhibition than throat swabs). Differential sample preparation from the same specimen has been done when testing separate single-species PCRs on BAL [De Barbeyrac et al., 1993]. A culture-enhanced PCR approach has also been suggested to overcome the effect of inhibitors in the amplification process [Abele-Horne et al., 1998].

In early 2000s, Loens et al.(2003) stated that the development and application of new nucleic acid amplification techniques (NAATs) in diagnostic mycoplasmology required proper validation and standardization, and performance of different NAATs must be compared with each other in order to define the most sensitive and specific tests. The NAATs have demonstrated their potential to produce rapid, sensitive and specific results, and are now considered the methods of choice for direct detection of *M. pneumoniae*, *M. genitalium*, and *M. fermentans* [Cassell et al., 1994a]. There is a great variation in methods used from study to study, including variability of target gene sequences (P1, 16S RNA, ATPase, *tuf*), assay format (single, multiplex) or technologies (Real-time PCR, NASBA) [Loens et al., 2003a, 2010]. Also, different specimens have been used, such as sputum, nasopharyngeal or pharyngeal swabs, bronchoalveolar lavages or pleural fluid, and then it is difficult to compare these data. A comprehensive review about the use of NAATs for the detection of *M. pneumoniae* in clinical samples was done by Loens et al., 2003b, 2010, and by Ieven, 2010. Table 3, shows a selection of primers sets developed in the 1990s for testing diverse clinical samples.

Organism	Primer sets	Sequence (5'→3')	Target	Amplicon size (bp)	Ref.
<i>Mollicutes-specific</i>	FW: GPO-1 RV: MGSO	ACT CCT ACG GGA GGC AGC AGT A TGC ACC ATC TGT CAC TCT GTT AAC CTC	rDNA 16S	715	Van Kuppeveld <i>et al.</i> , 1992
<i>M. fermentans</i>	FW: RW005 RV: RW004 IP: RW006	GGT TAT TCG ATT TCT AAA TCG CCT GGA CTA TTG TCT AAA CAA TTT CCC GCT GTG GCC ATT CTC TTC TAC GTT	IS-like element	206	Wang <i>et al.</i> , 1992
<i>M. genitalium</i>	FW: MGS-1 RV: MGS-2 IP: MGS-I	GAG CCT TTC TAA CCG CTG C GTG GGG TTG AAG GAT GAT TG AAG CAA CGT AGT AGC GTG AGC	MgPa adhesion gene	673	De Barbeyrac <i>et al.</i> , 1993
<i>M. hominis</i>	FW: MYCHOMP RV: MYCHOMN IP: MYCHOMS	ATA CAT GCA TGT CGA GCG AG CAT CTT TTA GTG GCG CCT TAC CGC ATG GAA CCG CAT GGT TCC GTT G	rDNA 16s	170	Grau <i>et al.</i> , 1994
<i>M. penetrans</i>	FW: MYCPENETP RV: MYCPENETN IP: MYCPENETS	CAT GCA AGT CGG ACG AAG CA AGC ATT TCC TCT TCT TAC AA CAT GAG AAA ATG TTT AAA GTC TGT TTG	rDNA 16s	407	Grau <i>et al.</i> , 1994
<i>M. pneumoniae</i>	FW: MP5-1 RV: MP5-2 IP: MP5-4	GAA GCT TAT GGT ACA GGT TGG ATT ACC ATC CTT GTT GTA AGG CGT AAG CTA TCA GCT ACA TGG AGG	Unknown gene	144	Bernet <i>et al.</i> , 1989
<i>Ureaplasma spp.</i>	FW: U5 RV: U4 IP: U9	CAA TCT GCT CGT GAA GTA TTA C ACG ACG TCC ATA AGC AAC T GAG ATA ATG ATT ATA TGT CAG GAT CA	Urease genes	429	Blanchard <i>et al.</i> , 1993
<i>U. parvum</i> <i>U. urealyticum</i>	FW: Uu-1 RV: Uu-2 IP: UUSO	TAA ATG TCG GCT CGA ACG AG GCA GTA TCG CTA GAA AAG CAA C CAT CTA TTG CGA CGC TA	rDNA 16s	311	Van Kuppeveld <i>et al.</i> , 1992
<i>U. parvum</i> <i>U. urealyticum</i>	FW: UMS-125 RV: UMA-226-	GTA TTT GCA ATC TTT ATA TGT TTT CG CAG CTG ATG TAA GTG CAG CAT TAA ATT C	MBA gene	402,403 (Up) 443 (Uu)	Kong <i>et al.</i> , 1999

bp, Base pairs; FW, Forward; RV, Reverse; IP, Internal probe.

Table 3. Selected primer sets used for detection of mycoplasmas in clinical specimens

6. Treatment and prevention

Due to absence of the cell wall envelope, mycoplasmas are insensitive to β -lactam antibiotics. However, antibiotics targeting protein synthesis or DNA modification molecules are highly effective against these bacteria. Macrolides, tetracyclines and fluoroquinolones eliminate mycoplasmas efficiently both *in vivo* and *in vitro* [Cassell *et al.*, 1994a; Waites *et al.*, 2000, 2008].

Mycoplasma infections in the upper respiratory tract are usually self-limiting, so antibiotic treatment is not generally recommended, even though some clinicians recommend it to prevent the risk of recurrence of respiratory illness [Waites & Talkington, 2004]

The antimicrobial of choice for treating lower respiratory tract *M. pneumoniae* infections are the macrolides in both adults and children. Patients receiving macrolides of recent generation showed improved tolerance, require fewer doses and have shorter treatment duration than older compounds. However, empirical antimicrobial treatment for *M. pneumoniae*-infected ambulatory patients is more practical; hence if hospitalization is required and/or patient has underlying risk factor, antimicrobial susceptibility testing is recommended. Use of tetracycline and fluoroquinolones is restricted to treat adult patients and should not be used in children aged <8 years [Cassell et al., 1994a; Waites et al., 2000]. A potential problem in the antimicrobial management of *M. pneumoniae* infections is the emergence of macrolide resistance [Atkinson et al., 2008; Waites et al., 2008].

The recovery of *Ureaplasma spp* and/or *M. hominis* in pure or mixed cultures from clinical specimens of symptomatic patients, in absence of associated biota, should be considered sufficient to initiate antimicrobial therapy. These microorganisms are resistant to sulfonamides and trimethoprim, and often exhibit resistance to aminoglycosides and chloramphenicol. *Ureaplasma spp* is resistant to clindamycin and susceptible to erythromycin, whereas *M. hominis* shows the opposite susceptibility profile. While tetracyclines are the antibiotics of choice for treating ureaplasma infections in adults, erythromycin therapy is recommended for neonates. In contrast, *M. hominis* infections other than central nervous system in children under 8 years of age can be treated with clindamycin [Cassell et al., 1994a; Waites et al., 2000, 2005].

Since strains from several mycoplasma species rapidly acquire resistance to antimicrobials, prevention of mycoplasma infections via chemoprophylaxis is not recommended [Razin et al., 1998].

6.1 Mycoplasma susceptibility testing

As antibiotic-resistant strains of mycoplasmas have appeared and become more common, antibiotic susceptibility testing for these microorganisms has become important. [Roberts, M.C., 1992]. However there are no official guidelines for performance, interpretation, or quality control of *in vitro* susceptibility tests for human mycoplasmas [Waites & Talkington, 2004].

The broth dilution method is the most widely used. Prior to test, pure cultures should be passage in appropriate broth and the color-changing units (CCU) or colony-forming units (CFU) quantitative method. For the assay, bacterial cultures should be adjusted to 1000 – 10000 CCU in 0.2 mL, followed by a 2-hour incubation at 37°C, to begin active growth. The broth microdilution assay involves the addition of 100-µL aliquots of adjusted cultures to wells 2 – 12, then 100 µL of broth containing the highest concentration of the antibiotics is added to wells 1 and 2, followed by 2-fold serial dilutions up to well 12 (concentration range 256-0.008 µg/mL). Positive and negative controls should be included. The initial minimal inhibitory concentration (MIC) is defined as the lowest dilution of antibiotic in which metabolism of the organism is inhibited, as evidenced by lack of color change in the media at the time the control organism well first shows color change. Presumptive MICs for ureaplasmas will be available at 16 to 24 h and those for *M. hominis* will be at 36 to 48 h but *M. pneumoniae* may require 5 days or more until evidence of grow in the control wells is evident [Cassell et al., 1994a; Waites et al., 2000].

There are commercial kits for mycoplasma susceptibility testing such as: Mycoplasma IST, Mycoplasma SIR, Mycofast “All In”, and MYCOKIT ATB, although they are available only in Europe.

Reports of macrolide resistance in *M. pneumoniae* strains have been published since the past decade. These resistant strains were shown to possess gene mutations in the 23S rRNA. The impact of macrolide resistance on the clinical course of infections is still unclear, but PCR assays have been developed to detect some of these mutations in order to identify these resistant strains [Atkinson et al., 2008].

Tetracycline resistance among *Ureaplasma spp* and *M. hominis* isolates can be distinguished by broth- or agar-based methods since the resistant strains consistently have MICs of ≥ 8 $\mu\text{g}/\text{mL}$ whereas susceptible strains have MICs of ≤ 2 $\mu\text{g}/\text{mL}$, with no overlapping between the two populations [Waites et al., 2000; Cassell et al., 1994a]. Tetracycline resistance among *M. hominis* and *Ureaplasma spp.* isolates has been associated with the presence of Tet M determinant which codes for production of a ribosome-binding protein that prevents tetracycline binding to ribosomes [Roberts, M.C., 2002].

6.2 Vaccines

The initial vaccine candidate for *M. pneumoniae* was formalin-inactivated bacteria, but their protective efficacy results were generally disappointing, since some immunized volunteers developed more severe illness after experimental challenge with live mycoplasmas. Development of live attenuated vaccines never made it to human use due to concern over residual virulence of the vaccine strain of *M. pneumoniae* [Waites et al., 2008]. Other vaccine candidates have included acellular protein and polysaccharide components and recombinant DNA. While the importance of the P1 adhesin in mediating *M. pneumoniae* cytoadherence and initiation of disease cannot be denied, animal studies using P1 as a vaccine antigen have not demonstrated protective efficacy [Razin et al., 1998; Waites & Talkington, 2004].

As higher rates of surface antigenic variation among several human mycoplasmas have been described, whenever promising antigens are selected as vaccine candidates they are rapidly discarded. The three types of antigenic variation are: 1) Phase variation, a feature involving selective turning on/off of gene transcription; 2) Size variation as a result of variation in the number of tandem repeats near the 5' end; and 3) Differential masking of surface antigens by the lipid moiety of lipoproteins [Chambaud et al., 1999; Momynaliev & Govorun, 2001].

The availability of the full genome sequences of several human mycoplasmas, will allow better understanding of the structure and functionality of these bacteria, including virulence factors and immunogenic molecules.

7. Concluding remarks

It is undeniable the ability of *Mycoplasma pneumoniae* and *Ureaplasma spp.* to cause pneumonia. Other mycoplasma species are potential respiratory pathogens, especially in conjunction with immune compromise. There is strong evidence that mycoplasmal respiratory infections elicit inflammatory responses that can result chronic lung injury both in adults and neonates. Improvement of laboratory methods for research and diagnostic purposes in mycoplasmaology has allowed establishing associations with pulmonary diseases such as COPD, asthma, and BPD. However additional work must be done for prevention, treatment strategies and vaccine development.

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Corresponding author: Dra. Silvia Giono-Cerezo. Laboratorio de Bacteriología Médica, Departamento de Microbiología, ENCB-IPN. Carpio y Plan de Ayala S/N, Col. Casco de Sto. Tomás, C.P. 11340, México D.F. México. Phone: +52(55)57296300 ext. 62374.

Email: sgiono@yahoo.com

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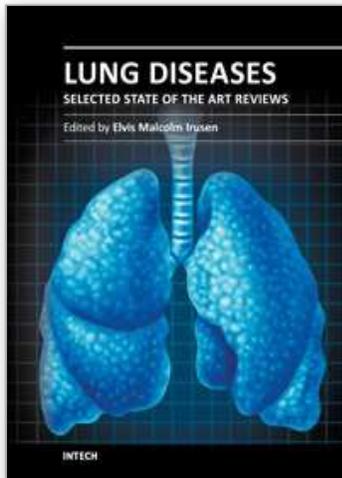
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The developments in molecular medicine are transforming respiratory medicine. Leading clinicians and scientists in the world have brought their knowledge and experience in their contributions to this book. Clinicians and researchers will learn about the most recent advances in a variety of lung diseases that will better enable them to understand respiratory disorders. This treatise presents state of the art essays on airways disease, neoplastic diseases, and pediatric respiratory conditions. Additionally, aspects of immune regulation, respiratory infections, acute lung injury/ARDS, pulmonary edema, functional evaluation in respiratory disorders, and a variety of other conditions are also discussed. The book will be invaluable to clinicians who keep up with the current concepts, improve their diagnostic skills, and understand potential new therapeutic applications in lung diseases, while scientists can contemplate a plethora of new research avenues for exploration.

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