# BACTERIOLOGY - CHAPTER NINETEEN

# MYCOPLASMA AND UREAPLASMA

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**TEACHING OBJECTIVES**

To describe the morphological and physiological characteristics of the mycoplasmas

To discuss the pathogenesis of mycoplasma infections

To describe the clinical syndromes associated with and the epidemiology, diagnosis and treatment of mycoplasma infections

**KEY WORDS**
T-strains
"Fried Egg" Colonies
P1 Adhesin
Primary Atypical Pneumonia
Walking Pneumonia
Cold Agglutinins

The family *Mycoplasmataceae* contains two genera that infect humans: *Mycoplasma* and *Ureaplasma*, which are usually referred to collectively as mycoplasmas. Although there are many species of mycoplasmas, only four are recognized as human pathogens; *Mycoplasma pneumoniae, Mycoplasma hominis, Mycoplasma genitalium,* and *Ureaplasma urealyticum*. Although there are other species that have been isolated from humans, their role in disease is not well established. The diseases caused by *M. pneumoniae, M. hominis, M. genitalium* and *U. urealyticum* are presented in Table 1 (Adapted from: Murray, *et al.*, Medical Microbiology 3rd Ed., Table 42-1).

**Table 1**

| Organism | Disease |
|---|---|
| *M. pneumoniae* | Upper respiratory tract disease, tracheobronchitis, atypical pneumonia |
| *M. hominis* | Pyelonephritis, pelvic inflammatory disease, postpartum fever |
| *M. genitalium* | Non-gonococcal urethritis |
| *U. urealyticum* | Non-gonococcal urethritis |

## Morphology and Physiology

The mycoplasmas are the smallest free-living bacteria. They range from 0.2 - 0.8 micrometers and thus can pass through some filters used to remove bacteria. They have the smallest genome size and, as a result, lack many metabolic pathways and require complex media for their isolation. The mycoplasmas are facultative anaerobes, except for *M. pneumoniae*, which is a strict aerobe. A characteristic feature that distinguishes the mycoplasmas from other bacteria is the lack of a cell wall. Thus, they can assume multiple shapes including round, pear shaped and even filamentous.

The mycoplasmas grow slowly by binary fission and produce "fried egg" colonies on agar plates (Figure 1a); the colonies of *M. pneumoniae* have a granular appearance. Due to the slow growth of mycoplasmas, the colonies may take up to 3 weeks to develop and are usually very small. The colonies of *Ureaplasma* are extremely small and thus *Ureaplasma* are also called T-strains (tiny strains).

Figure 1a Gram-negative *Mycoplasma hominis*, and T-strain Mycoplasma isolates, which had been grown on agar medium. Members of the genus Mycoplasma lack a cell wall, and are therefore, difficult to treat with many antibiotics, which have a negative affect on bacterial cell-wall synthesis such as penicillin. CDC

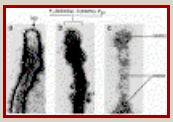
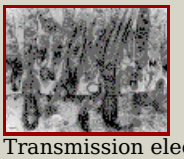
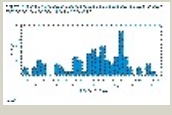


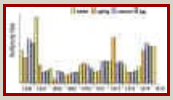
Figure 1b Transmission electron photomicrographs of the specialized tip organelle of cytadherence-positive M. pneumoniae demonstrating a) truncated structure with nap, b) clustering of cytadherence-related proteins (P1, B, C, P30) at the tip based on immunolabeling with ferritin and colloidal gold and crosslinking studies, and c) Triton X-100-resistant, cytoskeleton-like, structure with distinct bleb and parallel filaments



Transmission electron photomicrograph of a hamster trachea ring infected with M. pneumoniae. Note the orientation of the mycoplasmas through their specialized tip-like organelle, which permits close association with the respiratory epithelium. M, mycoplasma; m, microvillus; C, cilia. Both images used with permission. From Baseman and Tully, Emerging Infection Diseases 3



Acquired Pneumonia Caused by Mycoplasma pneumoniae -- Colorado, 2000



Infections of children under 15 years of age in Seattle between 1969 and 1975. (From: Foy, *J Infect Dis.* 139, 681, 1979. Redrawn from : Murray, *et al.*, Medical Microbiology, 3rd Ed).

The mycoplasma all require sterols for growth and for membrane synthesis. The three species can be differentiated by their ability to metabolize glucose (*M. pneumoniae*), arginine (*M. hominis*) or urea (*U. urealyticum*). The fourth species *M. genitalium* is extremely difficult to culture.

## Pathogenesis

### Adherence factors

The mycoplasmas are extracellular pathogens that adhere to epithelial cell surfaces. Thus, adherence proteins are one of the major virulence factors. The adherence protein in *M. pneumoniae* has been identified as a 168kD protein called P1. The P1 Adhesin localizes at tips of the bacterial cells and binds to sialic acid residues on host epithelial cells (Figure 1b)

The nature of the adhesins in the other species has not been established. Colonization of the respiratory tract by *M. pneumoniae* results in the cessation of ciliary movement. The normal clearance mechanisms of the respiratory tract do not function, resulting in contamination of the respiratory tract and the development of a dry cough.

### Toxic Metabolic Products

The intimate association of the mycoplasma and the host cells provides an environment in which toxic metabolic products accumulate and damage host tissues (Figure 1). Both hydrogen peroxide and superoxide, which are products of mycoplasma metabolism, have been implicated in pathogenesis since oxidized host lipids have been found in infected tissues. Furthermore, the mycoplasmas have been shown to inhibit host cell catalase, thereby increasing the peroxide concentrations.

### Immunopathogenesis

Mycoplasmas can activate macrophages and stimulate cytokine production and lymphocyte activation (*M. pneumoniae* is a superantigen). Thus, it is has been suggested that host factors also contribute to pathogenesis. Experimental evidence in animals supports this suggestion. Ablation of thymus function before infection with *M. pneumoniae* prevents the development of pneumonia and animals in which thymic function is restored develop pneumonia at an exacerbated rate. Epidemiologic data in humans suggest that repeated infections are required before clinical disease is observed, again suggesting a role for host related factors in pathogenesis; most children are infected from 2 - 5 years of age but disease is most common in children 5-15 years of age.

## *M. pneumoniae*

### Epidemiology

Pneumonia caused by *M. pneumoniae* occurs worldwide and no increased seasonal activity is seen. However, epidemics occur every 4 - 8 years (Figure 2).

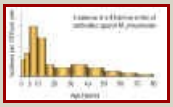
The disease is spread by close contact via aerosolized droplets and thus is most easily spread in confined populations (*e.g.*, families, schools, army barracks). The disease is primarily one of the young (5 - 15 years of age - Figure 3)

### Clinical syndrome

The most common clinical syndrome following infection with *M. pneumoniae* is tracheobronchitis, which is seen in 70-80% of the infections. Approximately one third of infected persons will develop pneumonia which is usually mild but of long duration. Pneumonia caused by this agent has been referred to a 'primary atypical pneumonia' and 'walking pneumonia'. The clinical course of the disease is depicted in Figure 4

The incubation time following infection is approximately 2 - 3 weeks at which time fever, headache and malaise are gradually observed. These symptoms may be

**Figure 2**



Antibody titers in different age groups. Anti-*mycoplasma pneumoniae* antibodies indicate pneumonia caused by this organism is highest in the 5-15 year age group (From: Foy, *J Infect Dis.* 139, 681, 1979. Redrawn from: Murray, *et al.*, Medical Microbiology, 3rd Ed).

**Figure 3**

WEB RESOURCES

Mycoplasmas: Sophisticated, Reemerging, and Burdened by Their Notoriety
From Emerging Infectious Diseases

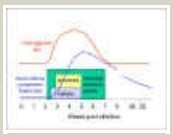


Figure 4

accompanied by a persistent non-productive hacking cough. Respiratory symptoms appear somewhat later and persist for several weeks. Interestingly, in *M. pneumoniae* pneumonia X-ray examination will show signs of pneumonia even before respiratory symptoms appear. Organisms can be cultured from sputum before symptoms occur and throughout the course of the disease. Resolution of the disease is slow but it is rarely fatal. The disease must be differentiated from other 'atypical' pneumonias.

### Immunity

Complement activation via the alternative pathway and phagocytic cells both play a role in resistance to infection. As the infection proceeds, antibodies play a role in controlling infection, particularly IgA. The development of delayed type hypersensitivity, however, is associated with the severity of the disease, which supports the suggestion that pathogenesis is at least, in part, immunopathogenesis.

### Laboratory Diagnosis

In the early stages of infection diagnosis must be made on clinical grounds. However, as the infection progresses several laboratory tests are available.

- Microscopy
  This is not particularly useful because of the absence of a cell wall but it can be helpful in eliminating other possible pathogens.

- Culture
  Sputum (usually scant) or throat washings must be sent to the laboratory in special transport medium. It may take 2 -3 weeks to get a positive identification. Culture is essential for a definitive diagnosis.

- Serology

  - Complement fixation test - There is a good complement fixation test that has good sensitivity and specificity. However, the titers do not peak until 4 - 6 weeks after infection (Figure 4). A fourfold rise in titer is indicative of a recent infection. Since antibodies may persist for up to 1 year, a sustained high titer does not necessarily indicate a current infection.

  - Cold agglutinins - Approximately 34% - 68% of patients with *M. pneumoniae* infection develop cold agglutinins. Cold agglutinins are antibodies that agglutinate human erythrocytes at 4 degrees C but not at 37 degrees C. The antigen to which the antibodies are directed is the I antigen. These antibodies arise before the complement fixing antibodies and they decline faster (Figure 4). Cold agglutinins are not specific for *M. pneumoniae* infections, they can also appear in other infections and in other diseases (*e.g.* Infectious mononucleosis, influenza infections, cold agglutinin disease, leukemia). However, if present in a patient with clinical signs of *M. pneumoniae* infection, a presumptive diagnosis can be made.

  - ELISA - There is a new ELISA for IgM that has been used for diagnosis of acute infection. It is sensitive and specific. However, it is not yet commercially available.

### Treatment and Prevention

Since *mycoplasmas* lack a cell wall, the penicillins and cephalosporins are ineffective. The antibiotics of choice are tetracycline (adults only) and erythromycin. Prevention is a problem due to the long duration of the disease. It is problematic to isolate patients to avoid close contact for a long period of time. No vaccines are currently available.

## *M. hominis* and *U. urealyticum*

### Clinical syndromes

*M. hominis* is associated with pyelonephritis, pelvic inflammatory disease and post-partum fevers. *U. urealyticum* is associated with non-gonococcal urethritis.

## Epidemiology

Colonization with *M. hominis* and *U. urealyticum* can occur during birth but in most cases the infection will be cleared. Only in a small number of cases does colonization persist. However, when individuals become sexually active, colonization rates increase. Approximately 15% are colonized with *M. hominis* and 45% - 75% with *U. urealyticum*. The carriers are asymptomatic but the organisms can be opportunistic pathogens.

## Laboratory Diagnosis

Laboratory diagnosis is by culture.

## Treatment and Prevention

Since *mycoplasmas* lack a cell wall, the penicillins and cephalosporins are ineffective. The antibiotics of choice are tetracycline (adults only) and erythromycin. Abstinence or proper barrier protection are means of prevention.

 Return to the Bacteriology Section of Microbiology and Immunology On-line

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