MYCOPLASMA AND UREAPLASMA

Prof. Muhammad Akram Hossain
MMC
Each year an estimated 2 million cases and 100,000 pneumonia-related hospitalizations occur in the United States.
The name *Mycoplasma*, from the Greek *mykes* (fungus) and plasma (formed).

Eaton and colleagues cultured the causative agent of human primary atypical pneumonia (PAP) or 'walking pneumonia.' in 1940.

The ability to grow Eaton's Agent, now known as *Mycoplasma pneumoniae*, in cell free media allowed an explosion of research into what had overnight become the most medically important mycoplasma and what was to become the most studied mycoplasma.
Many pediatricians still consider mycoplasmas an uncommon cause of disease. Infectious diseases are often identified by "culturing" them--taking a small sample of tissue or fluid and keeping it in an incubator for a while to see what grows. Mycoplasmas are very tiny, shape-shifting, slow-growing critters that don't often show up on cultures.

But newer, more sensitive antibody tests prove mycoplasmas to be a common cause of infection. Over 40% of children have had a mycoplasma infection by their first birthday, more than 65% by age 5 years, and 97% by adulthood.
In addition to pneumonia, mycoplasmas can cause a variety of other respiratory illnesses, including ear infections (about 12% of all ear infections), sinus infections, bronchitis, croup, bronchiolitis, severe sore throats, infectious asthma, and even a version of the common cold. Most mycoplasma infections are not very severe but last for quite a long time.
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:
1. *Mycoplasma pneumoniae*,
2. *Mycoplasma hominis*,
3. *Mycoplasma genitalium*, and
4. *Ureaplasma urealyticum*.

Although there are other species that have been isolated from humans, their role in disease is not well established.
M. Pneumoniae
• Upper respiratory tract disease,
• Tracheobronchitis, atypical pneumonia

M. Hominis
• Pyelonephritis, pelvic inflammatory disease,
• Postpartum fever

M. Genitalium  Nongonococcal urethritis

U. Urealyticum  Nongonococcal urethritis
- Mycoplasma pneumonia is generally mild and does not require hospitalization; hence, the name "walking pneumonia".
Mycoplasma are small bacteria that do not contain a cell wall. They are difficult to grow in culture media and their growth is slow. They are unidentifiable in gram stains of sputum samples.
In 1938,
  - Reimann, detected first case of mycoplasma pneumonia

In 1943
  - Peterson discovered cold agglutinin

In 1944
  - Eaton discovered the bacteria (originally thought to be virus)
In the US:

- Infections with *M. pneumoniae* result in pneumonia in only 3% of cases;
- 20% of infections are asymptomatic,
- while 77% involve the upper respiratory tract.
- Epidemics of mycoplasmal pneumonia tend to occur every 4-8 years in the general population and tend to be more frequent within closed populations, such as in military and prison populations.
Mortality/Morbidity: In almost all patients, the pneumonia resolves without any serious complications.

Sex: The incidence is higher in males than females.

Age: Mycoplasmal pneumonia is common all age groups; however, it is most common in the first 2 decades of life and is rare in children younger than 4 years.
Smallest free-living bacteria
- No cell wall
- Cell membrane contains sterols
- Resistant to antibiotics that disrupt cell wall synthesis
- Pleomorphic filaments .1-.3 um in diameter that can pass through .45um filters
Mycoplasmas are facultative aerobes except *M. pneumoniae* which is strict aerobe
- Require sterols in medium
- Grow slowly-1-6 hours
- Small colonies
- Membrane contains a lot of glycolipids which in some cases cross-react with human tissues
The mycoplasmas grow slowly by binary fission and produce "fried egg" colonies on agar plates;
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).
Extracellular pathogen

- Adheres to glycoprotein receptors at the base of cilia on the respiratory epithelial cell surface
- Ciliostasis
- Epithelial cells damaged
- Normal clearance mechanisms disrupted
- Lower respiratory tract becomes irritated
$M. \textit{pneumoniae}$ - superantigen
- Stimulates influx of inflammatory cells
- Release of TNF-alpha and IL-1 more than IL-6
  - Results in clearance of organisms and pathology
**A. 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.

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.
Pathogenesis

B. 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. 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.
c. 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. Most children are infected from 2 - 5 years of age but disease is most common in children 5-15 years of age.
Pneumonia caused by *M. pneumoniae* occurs worldwide and no increased seasonal activity is seen. However, epidemics occur every 4 - 8 years.

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).
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 incubation time following infection is approximately 2 - 3 weeks at which time fever, headache and malaise are gradually observed. These symptoms may be 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.
In the early stages of infection diagnosis must be made on clinical grounds. However, as the infection progresses several laboratory tests are available.

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

2. **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

a. Complement fixation test - 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.

b. 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. 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). However, if present in a patient with clinical signs of *M. pneumoniae* infection, a presumptive diagnosis can be made.

c. 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.
Culture-2-6 weeks before positive, insensitive and not available in most labs
Specimen-throat washings, sputum
Growth requires special medium supplemented with serum (cholesterol)
Colonies are small-fried egg appearance under microscope
Ureaplasma requires urea for growth
Serology-only available for *M. pneumoniae*

- Complement fixation
  - Detects IgA
  - Occurs early after onset of infection
  - Peaks after 4 weeks
  - Persists for 6-12 months
  - Good sensitivity
  - False positives
Serology
- ELISA
  - Easier to perform than complement fixation
  - Good sensitivity
  - False positives
Serology

- Cold agglutinins
  - Non specific
  - Measures IgM antibodies to membrane glycolipids that cross react to the I antigen on human erythrocytes
  - Not very sensitive
  - False positives
Serology
- Serum cold agglutination is a nonspecific test for *M. pneumoniae*, but findings are positive in 50-70% of patients after 7-10 days of infection.
- A negative result does not exclude infection, and this test may be affected by cross-reactions with other pathogens, such as adenovirus, Epstein-Barr, and measles viruses.
- Other serological tests include complement fixation, enzyme-linked immunoassay, and indirect hemagglutination. All of these have acceptable sensitivity and specificity.

Polymerase chain reaction
- Work concerning the use of PCR in diagnosing *M. pneumoniae* with DNA is being performed.
- A radiolabeled DNA probe detects *M. pneumoniae* ribosomal RNA in respiratory secretions with 90% sensitivity.
- The WBC count generally is not helpful, since results may be normal or elevated. Hemolytic anemia has been described, but it is rare.

- Sputum Gram stains and cultures usually are not helpful, except in excluding other pathogens.

- Elevated erythrocyte sedimentation rates may be present.
Since mycoplasmas lack a cell wall, the penicillins and cephalosporins are ineffective. The antibiotics of choice are tetracycline (adults only) and erythromycin. M. pneumoniae - erythromycin, tetracycline

- U. ureaplasma - may be resistant to tetracycline. Treat with erythromycin or spectinomycin.

- M. hominis - resistant to erythromycin and sometimes to tetracycline. Treat with clindamycin
Prevention and Control

- Spread by close contact-prolonged infectivity makes isolation impractical
- No effective vaccines
- Protective immunity not seen

- *M. hominis, M. genitalium, U. ureaplasma* – avoid sexual contact, barrier protection
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.
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.
True/False

Mycoplasma and Ureaplasma are the smallest free-living bacteria _________.
Mycoplasma cell membranes contain sterols ___________.
Mycoplasmas form pleomorphic filaments _________.
Mycoplasmas lack a cell wall ___________.
*M. pneumoniae* attaches to the respiratory epithelium ___________.
The binding of *M. pneumoniae* to epithelial cells leads to ciliostasis and eventual loss of ciliated epithelial cells ___________.
*M. pneumoniae* acts as a superantigen ___________.
*M. pneumoniae* is transmitted by aerosolized droplets ___________.
*M. pneumoniae* primarily infects geriatric populations ___________.

Prof. Muhammad Akram Hossain, Mycoplasma
Practice questions

True/False

- *M. pneumoniae* causes a upper respiratory infection ________.
- *M. pneumoniae* causes a lower respiratory infection ________.
- *M. genitalium* causes a nongonococcal urethritis _____________.
- *M. hominis* causes pyelonephritis ________________.
- *M. hominis* causes pelvic inflammatory disease _____________.
- *M. hominis* causes postpartum fever ________________.
- *U. urealyticum* causes urethritis ________________.
- Complement fixation and/or ELISA based tests are available for *M. pneumoniae* ____________.
- *M. pneumoniae* infections can be treated with erythromycin and tetracycline ____________.
- *M. pneumoniae* infections can be treated with penicillin ____________.
"Pass on knowledge from me even if it is only one verse"

-Prophet Muhammad (peace be upon him)

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