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# *Mycoplasma pneumoniae* Respiratory Disease Symposium: Summation and Significance

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The symposium on *M. pneumoniae* respiratory disease has examined the clinical expression of infection in adults and children, the pathophysiologic disturbances which occur, and the laboratory diagnosis by isolation and serology. That these infections are very common has been well documented; however, a variable incidence over periods of several years tends to minimize importance of the disease for many clinicians. While good laboratory diagnostic methods exist, they provide retrospective insight predominantly and are not useful for early diagnosis or therapeutic decision making. Development of rapid diagnostic methods which are sensitive and specific is an important goal for future research. Success would facilitate our understanding and control of *M. pneumoniae* disease.

The importance of *Mycoplasma pneumoniae* as a cause of human respiratory disease has been well documented by epidemiologic studies in various settings in many countries [1]. In a metropolitan survey, the occurrence of mycoplasma pneumonia varied from 0.5-2.6/1,000 population/year, depending upon the age groups involved [2]; relative to the total occurrence of pneumonia in the same population, *M. pneumoniae* was responsible for between 5.7 and 28.4 percent of all cases. As shown in Table 1, it can be estimated from other studies that the syndrome of tracheobronchitis is 23 times more frequent than is pneumonia, and that 20 percent of the mycoplasma infections are asymptomatic. Extrapolated to the present population of the United States, these data would indicate that there are 500,000 cases of pneumonia and 11,500,000 cases of tracheobronchitis within a total of 15,000,000 infections by *M. pneumoniae* annually!

Despite the presence of data from surveillance and family studies indicating the high frequency of *M. pneumoniae* infections, clinicians diagnose the disease only occasionally, especially those with hospital-based medical practices. There are many reasons for this discrepancy. The mild nature of many cases does not compel patients to seek medical attention; those who report are seen most often in ambulatory primary care facilities where their symptoms and signs are so non-specific that *M. pneumoniae* is not considered and only symptomatic treatment is prescribed. Cases recognized during the occurrence of epidemic peaks tend to be forgotten during the next few years when only endemic disease occurs.

As indicated before, the most frequent clinical presentation of *M. pneumoniae* infection is the syndrome of tracheobronchitis associated with an influenza-like illness. This type of illness is a rather nondescript clinical entity which includes a cough



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TABLE 1
*Mycoplasma pneumoniae* in the United States

| Syndrome | Incidence/year[a] | Total Cases[b] |
|---|---|---|
| Pneumonia | 2/1,000[1] | 500,000 |
| Tracheobronchitis | 46/1,000[2] | 11,500,000 |
| Asymptomatic infections | 12/1,000[3] | 3,000,000 |
| All Infections | | 15,000,000 |

[a]Extrapolations based on:
[1]Alexander, et al: New Eng J Med 275:131, 1966
[2]Chanock, et al: JAMA 175:213, 1961
[3]Foy, et al: JAMA 197:137, 1966
[b]Estimated census of 250 million

together with other evidence of respiratory tract infection, such as fever, malaise, rhinorrhea, pharyngitis, sinusitis, and otitis media. One study in a pediatric practice population revealed the most common etiologic agents of tracheobronchitis to be respiratory syncytial virus, parainfluenza virus types 1 and 3, influenza viruses A and B, and *M. pneumoniae* [3]. Clinical differentiation of these agents was not possible except through consideration of epidemiologic features, particularly age of the patient and seasonal occurrence: most patients were older than four years, and outbreaks usually occurred between July and January. In this type of disease *M. pneumoniae* might be suspected if a concurrent epidemic were known, or if *M. pneumoniae* pneumonia had been diagnosed in a household contact of the patient with tracheobronchitis.

In patients presenting with pneumonia, as evidenced by pulmonary rales or dullness or by chest X-ray abnormalities, *M. pneumoniae* always should be considered among the etiologic possibilities because of its major contribution to the causation of pneumonia. Clinicians often think of conventional bacterial infections first in patients with pneumonia, probably because of the life-threatening consequences of these infections. Viral or mycoplasmal pneumonia may be considered secondarily and usually after efforts to exclude bacterial disease. Since it has been shown that viral and mycoplasmal pneumonias are indistinguishable by clinical and radiographic features [4], the practitioner is left with few valid criteria on which to base a primary diagnosis of mycoplasmal disease.

From the foregoing it is apparent that the diagnosis of *M. pneumoniae* disease may present a difficult problem for the practitioner. The following points, based on the state of knowledge which has been reviewed in this symposium, are suggested as guides (Table 2).

1. *M. pneumoniae* should be considered in all cases of pneumonia, since it is one of the more common etiologic agents. The frequency of mycoplasma pneumonia rivals the estimated occurrence of *Streptococcus pneumoniae* disease, which is the other common cause. Certain clinical characteristics make the likelihood of *M. pneumoniae* greater, including: patients of elementary school age, adolescents, or young adults; epidemics within families; and epidemics occurring outside the usual respiratory disease season, as in the summer and fall months. The disease has a very high incidence in closed population groups such as military recruits and university students [1].

2. The general clinical syndrome of *M. pneumoniae* disease is an influenza-like

TABLE 2
Diagnosis of *Mycoplasma pneumoniae* Disease

| |
|---|
| 1. Consider in all cases of pneumonia |
| 2. "Flu-like" febrile illness of gradual onset |
| 3. Symptoms of acute tracheobronchitis |
| 4. Paucity of physical findings |
| 5. Chest X-ray |
| 6. Exclude bacterial disease |
| 7. Cold hemagglutinin test |
| 8. Mycoplasma culture |
| 9. Mycoplasma serology |

illness with components of low-grade fever, headache, and lassitude. In true influenza disease the symptomatology develops rapidly, usually within 24 hours; in mycoplasmal disease the systemic manifestations develop more gradually over a period of several days. Many patients will have been symptomatic up to one week before seeking medical attention.

3. In addition to the systemic elements of illness, cough indicating the presence of tracheobronchitis is seen in most if not all *M. pneumoniae* infections. Initially the cough is dry, but later becomes productive of mucoid or muco-purulent sputum. Coughing may occur in paroxysms and often is worse in the evening, disturbing sleep.

4. *M. pneumoniae* disease often is accompanied by few physical signs, and the patients' complaints seem disproportionate to the observable evidence of infection. There may be slight erythema of the pharynx associated with complaint of a dry or scratchy sore throat. Rhonchi may be palpated or auscultated in the chest if sputum is being produced. The presence of rales, especially at the end of deep inspiration, should be sought with care since this finding would suggest pneumonia in this setting. Rarely are there sufficiently large areas of atelectasis or of pleural effusion to allow detection by physical examination.

Two other clinical syndromes should suggest the diagnosis of *M. pneumoniae* disease: the first is bullous myringitis, a painful red vesicular lesion of the tympanic membrane; the second is erythema multiforme exudativum (Stevens-Johnson syndrome) which involves both skin and mucus membranes. Neither bullous myringitis nor Stevens-Johnson syndrome occur exclusively with mycoplasma disease, but the diagnostic possibility is suggested by the numerous reports of these associations. No estimate of the incidence of these manifestions is available.

5. The chest X-ray is a very useful adjunct to the diagnosis of *M. pneumoniae* pneumonia, because of the limited physical findings outlined in item 4. Changes may precede the appearance of signs involving the lungs. The usual manifestations are increased peribronchial markings, generally involving one of the lower lobes. Associated perihilar streaking indicative of interstitial infiltration and areas of subsegmental atelectasis may be seen. Small, often transient collections of pleural fluid are not unusual. Emphasis has been placed on the most common X-ray presentation, but it should be mentioned that changes which mimic many other pulmonary disease processes can be encountered, making the diagnosis more obscure in some cases.

6. Once the diagnosis of *M. pneumoniae* disease is entertained, it can be strengthened by steps to exclude other possibilities. Useful aids are the peripheral

blood total and differential leukocyte counts which usually are normal; typically leukopenia occurs in viral syndromes, and leukocytosis in classical bacterial pneumonias. An exception may occur in patients with sickle cell disease, who have been reported to develop polymorphonuclear leukocytosis during mycoplasma pneumonia [5]. Bacterial cultures of peripheral blood or buffy coat may be helpful to exclude sepsis which can be secondary to bacterial pneumonia. Careful collection of historical information may remove some entities from the differential diagnostic list, for example, psittacosis, mycoses, tuberculosis, aspiration pneumonitis, and occupational lung disease.

7. A simple diagnostic procedure with may be helpful is the cold hemagglutinin test. These temperature-dependent agglutinins are present in about half of patients with *M. pneumoniae* pneumonia, developing late in the first or during the second week of symptoms and increasing fourfold or more in titer by the third week. The IgM-anti-I antigen antibodies which are responsible for the agglutination disappear in about six weeks. Because of their early appearance, cold hemagglutinins may be found when patients are first seen, and can be helpful for therapeutic decisions. High titers ($\geq$ 1:128) and fourfold rises (or falls) in titers between paired sera suggest *M. pneumoniae* infection. However, the reaction is not specific for mycoplasma disease since cold hemagglutinins occur in a variety of other conditions. If the reaction is negative, *M. pneumoniae* disease is not excluded. There are correlations between severity of pneumonia and higher cold hemagglutinin titers; antibiotic therapy tends to suppress the response.

A screening, or "bedside" cold hemagglutinin test is very useful clinically. As originally described [6], 0.2 ml patient blood is mixed with an equal volume of Na citrate solution in a small tube which is iced for 15 seconds. The tube is then tipped and rotated for inspection of the blood film. A positive test is indicated by floccular agglutination which disappears when the tube is warmed to 37°C. Quantitative studies have shown that a positive test indicates a standard method titer $\geq$ 1:64 [7].

8. The "gold standard" for diagnosis of mycoplasma pneumonia remains isolation of *M. pneumoniae* from sputum or respiratory tract secretions. Dr. Tully has provided evidence that the SP-4 formula first used to isolate *Spiroplasma mirum* [8] is a superior medium for recovering *M. pneumoniae* compared with earlier formulations. Development of improved media should augment our diagnostic ability. Unfortunately, isolation information is useful mainly in retrospect since time required (seven days–six weeks) is too long to assist therapeutic decisions.

9. Serological methods have been the most popular form of diagnosis for *M. pneumoniae* infections in recent years; necessary reagents have become commercially available, and few laboratories have the capability for isolation and identification procedures. The complement fixation method has enjoyed greatest use, although the specificity of the reaction is being questioned since the antigens involved are not unique to *M. pneumoniae*. Diagnostic results require comparisons of titers in acute and convalescent sera, making this another retrospective method. Due to the ubiquity of *M. pneumoniae* infections, measurable antibodies in single sera can indicate either current or prior infection and thus are not diagnostic. As discussed by Drs. Busulo and Meloni, use of newer techniques such as ELISA has merit in providing greater specificity and rapidity for sero-diagnosis. The measurement of *M. pneumoniae* specific IgM antibodies, as permitted by ELISA, also suggests active infection as opposed to IgG antibodies which may persist for a long time following infection.

From this review of our ability to recognize *M. pneumoniae* disease clinically, and to diagnose it in the laboratory, it becomes apparent that a major shortcoming is the lack of a sensitive and specific rapid diagnostic test. Many years ago Hers [9] described success using immunofluorescence with sputum samples, but no reports have appeared of the systematic application of this approach. The method could be difficult to apply to children who rarely are able to provide sputum specimens. As pointed out in a recent letter by Drs. Foy and Allan, "The most cogent reason for failure to recognize the importance of this agent is the lack of a rapid diagnostic test" [10]. If a simple procedure were available for clinical use, the many infections which masquerade as "non-specific tracheobronchitis" or as "viral syndrome" could be recognized and treated more effectively. Furthermore, increased recognition of infections can expand our understanding of the clinical features of the disease which were addressed earlier in detail by Drs. Niitu and Izumikawa. This in turn will facilitate greater understanding of the pathogenesis, including the clinical expression of the pathophysiologic disturbances which have been described by Dr. Yoshida. This symposium has served to provide a forum for discussion of many implications for the future concerning an important human respiratory disease.

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