The Incidence of *Mycoplasma pneumoniae* Pneumonia

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Background: *Mycoplasma pneumoniae* has been considered a pathogen for humans since the 1940s. Of the 12 species of *Mycoplasma* found in humans, *M pneumoniae* is the most widely recognized pathogen. Morbidity from *M pneumoniae* results from the combined direct effect of cytotoxins produced by the organisms and the indirect effect of inflammatory responses to the presence of the organisms. Several studies have reviewed the incidence of *M pneumoniae* pneumonia in selected populations with variable results. By using tests that were not definitive detectors of the organism, earlier studies cited have overestimated the true incidence of this infection. We reevaluate several of these early studies in the light of newer findings.

***Methods:* Using the key words "*Mycoplasma pneumoniae*," "pneumonia," "prevalence," "incidence," and "community acquired," the MEDLINE files from 1992 to the present were searched. Articles dating before 1992 were accessed from cross-reference of the more recent articles. Only clinical trials with a sample size greater than 125 were considered.**

***Results and Conclusions:* *M pneumoniae* pneumonia occurs in 4- to 5-year cycles and in densely populated areas. Clinical symptoms of *M pneumoniae* pneumonia include dry cough, sore throat, middle ear involvement, and low-grade fever, as well as additional extrapulmonary manifestations. Bullous myringitis is not a common finding in *M pneumoniae* infection. Diagnostic tests include cold agglutinins, complement fixation, culture, and enzyme immunoassay. A fourfold rise in *M pneumoniae*-specific antibody in serum from acutely ill and convalescent patients remains the reference standard for diagnosing the infection.**

The incidence of *M pneumoniae* is probably lower than reported in many studies. Using tests that are not diagnostic of the infection can give a falsely elevated incidence of *M pneumoniae* infection in specific populations. (J Am Board Fam Pract 1997;10:425-9.)

In 1898 Nocard and Roux[1] identified *Mycoplasma* as a cause of respiratory tract illness when they isolated a slowly growing organism from contagious bovine pleuropneumonia specimens. Later investigators referred to similar clinical isolates as pleuropneumonia-like organisms. Some investigators thought these organisms should be considered viruses because the organisms were smaller than any known bacteria. That the organisms could replicate extracellularly led to the correct conclusion that they were somewhat similar to bacterial L forms. In 1944 Eaton and associates[2] isolated the agent responsible for recruit pneumonia, which later became known as the Eaton agent. The organism was first observed by Liu,[3] who used immunofluorescent methods to document the organism in an infected chick embryo bronchus. Today the organism is known as the genus *Mycoplasma*.

Mycoplasma species belong to the class Mollicutes (soft skin), which comprises the smallest free-living microorganisms. Each of the 12 species of *Mycoplasma*[4] found in humans has a deformable triple-layered membrane (similar to the membrane that contains the cytoplasm of all bacteria and mammalian cells) that surrounds the cytoplasm. *Mycoplasma* species contain both DNA and RNA. Although *Mycoplasma pneumoniae* is

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resistant to β–lactam antibiotics,[4] which interfere with cell wall synthesis, it is highly sensitive to complement. Incubations of 5 to 20 days are necessary to grow *M pneumoniae* because the doubling time in vitro is 6 to 20 times slower than that of most bacteria.[4]

M pneumoniae is the most widely recognized pathogen of the 12 species of *Mycoplasma* found in humans.[4] A receptor on the cell membrane allows the organism to attach to diverse cell types, such as respiratory tract epithelia and red blood cells. In high concentrations the organisms inhibit the ciliary action of the respiratory epithelia and cause cell necrosis. The resulting morbidity is the combined direct effect of cytotoxins produced by the organisms and the indirect effect of inflammatory responses to the presence of the organisms. *M pneumoniae*-specific immunoglobulin (Ig) M and IgG antibodies play an important role in the ability of immunocompetent persons to eliminate (without the use of antimicrobial agents) the infection in 10 to 14 days. Although antimicrobial agents influence the course of illness, they do not eliminate the nasopharyngeal carriage stage.[5]

M pneumoniae is carried in respiratory droplets and is transmitted from an infected person in close contact with another person. The results of some studies[6] suggest *M pneumoniae* pneumonia is more prevalent in the autumn, but Foy et al[7] report that rates of *M pneumoniae* pneumonia do not vary with seasons. Distribution of the disease is worldwide. Evans et al[8] found that pneumonias caused by *M pneumoniae* in the population they studied appear to cycle every 4 to 5 years.

The role of *Mycoplasma* in immune-mediated disease is not entirely clear. Cimolai et al[9] describe 4 patients with severe bacterial or viral infections that occurred during or after *M pneumoniae* infection. They postulate that *M pneumoniae* can create an anatomic, physiologic, or immunologic environment that either facilitates invasiveness or enhances[7] local damage to cells. One immunologic explanation[10] of this damage is the antigenicity of mycoplasmal lipid-associated membrane proteins that are exposed on the cell surface. The host's response to these antigens can lead to an immune-mediated set of symptoms. In patients who have acquired immunodeficiency syndrome, mycoplasmal infections could enhance the pathogenicity of human viruses, including human immunodeficiency virus type 1.[10]

Methods

We began this study when we found that our clinical practice experience of the incidence of *M pneumoniae* infection did not correlate with what we had been led to believe by the literature on this subject. Using the key words "*Mycoplasma pneumoniae*," "pneumonia," "community acquired," "prevalence," and "incidence," the MEDLINE files from 1992 to the present were searched. Articles dating before 1992 were accessed from cross-reference of the more recent articles. Only clinical trials with a sample size greater than 125 were considered. A major clinical laboratory was also contacted to ascertain the experience that it had with tests specific for *M pneumoniae* infection.

Incidence

Evans et al[8] studied University of Wisconsin students admitted to the student infirmary between 1960 and 1965. The authors diagnosed 204 cases of pneumonia between 1953 and 1965 and tested the serum from 67 of these patients with a complement fixation test. Forty-three (64.2 percent) had a fourfold rise in complement fixation titer, but we cannot assume this percentage would persist for the other 137 cases of pneumonia. One-hundred fifteen patients were tested with throat cultures of which 51 (44.3 percent) were positive for *M pneumoniae*. Their finding of a 51.7 percent incidence of *M pneumoniae* infection in pneumonia was based on the false assumption that throat cultures positive for *M pneumoniae* correlated with disease. The data are not presented accurately enough to reach any meaningful conclusions, and the authors mistakenly placed diagnostic importance on positive throat cultures.

Foy et al[7] also used positive throat cultures as a diagnostic determinant. They studied patients with pneumonia in the Group Health Cooperative of Puget Sound, a prepaid medical care group with 85,000 members distributed throughout Seattle and nearby areas. The studies were done during a 5-year period (1963 to 1968) and utilized throat swabs and paired blood specimens for diagnosis of *M pneumoniae* infection. The throat swabs and paired blood specimens were taken from 48 percent and 24 percent of patients with pneumonia, respectively. They estimated the number of patients with *M pneumoniae* pneumonia by adding the number of patients with a fourfold rise in anti-

body titer to *M pneumoniae* and the number of patients with *M pneumoniae* isolated from throat swabs. This sum was divided by the total number of all pneumonias to determine the percentage of pneumonias caused by *M pneumoniae*.

There were 5442 diagnosed cases of pneumonia; 385 (15 percent) of 2604 swabs from these cases yielded *M pneumoniae*, and 223 (14 percent) of 1593 serum specimens from these cases yielded a fourfold rise in antibody titer. Foy et al added the number of positive throat cultures (229 without positive sera) and arrived at a 20 percent incidence of *M pneumoniae* pneumonia. In a report published 21 years later, however, Gnarpe et al[11] concluded that Foy et al should have used only the number of patients with a fourfold rise in antibody titer (233) divided by the number of patients from whom paired serum samples were collected (1593). The resulting incidence would have been 15 percent, which after age standardization would have been closer to 10 percent.

In the past, the incidence of *M pneumoniae* pneumonia could have been overestimated because throat cultures positive for the organism do not necessarily correlate with the presence of the disease. In their 1992 report, Gnarpe and colleagues[11] found that the throats of 102 (13.5 percent) of 758 healthy volunteers were colonized with *M pneumoniae*. This initial phase of their study was conducted between February 1989 and May 1990 and was completed during an epidemic of pneumonia. The results of continued study from September 1990 to July 1991 showed that *M pneumoniae* was isolated from the throats of only 23 (4.6 percent) of 499 healthy volunteers. The authors concluded that a positive *M pneumoniae* culture does not necessarily constitute evidence of disease, and that positive results from a throat culture should be confirmed by a fourfold rise in complement fixation titer.

In 1991 King and Muncie[12] studied 187 patients from a rural family practice in North Carolina who had respiratory tract symptoms with both IgM and IgG antibodies to *M pneumoniae* by using a latex agglutination test (m-Clone, Access Medical Systems, Branford, Conn). Ninety-seven patients without respiratory tract symptoms were tested as a control group. The m-Clone *Mycoplasma* test results were positive in 43 percent of patients who had symptoms and in 7 percent of patients who did not have symptoms. The results of this rapid latex agglutination test were not compared with those of complement fixation tests (a reference standard), so there is little to infer from the results that were obtained. Because of the variation in IgG and IgM antibodies in all persons and the small number of patients sampled, it is difficult to draw conclusions about the incidence of *M pneumoniae* infection in the general population from this study. The authors admitted this difficulty in their research; not all patients with respiratory symptoms were tested because of inadequate staff, and the study was limited to one site and one season.

In a 1991 review article, Luby[5] reported that in four published studies of patients hospitalized with pneumonia, an average of 7 percent of the patients had pneumonia caused by *M pneumoniae*. In 1993, Marrie[13] reported that only 13 percent of persons with *M pneumoniae* infection develop pneumonia.

Clinical Manifestations

The clinical symptoms of *M pneumoniae* pneumonia include nonproductive cough (97 percent of the patients), sore throat (52 percent), middle-ear involvement (20 percent), and low-grade fever (85 percent).[14] Physical findings can vary widely and can include scattered rales and ronchi, throat infection, and cervical adenopathy. Thirty-three percent of patients have extrapulmonary manifestations that include gastrointestinal (42 percent), musculoskeletal (24 percent), dermatologic (6 percent), cardiac (33 percent), and neurologic symptoms (7 percent).[14]

In 1980 Roberts[15] reported in a critical review of the literature that only 1 (1.5 percent) of 66 needle aspirates of the middle ear or bleb in bullous myringitis was culture-positive for *M pneumoniae*. When these 66 aspirates were routinely cultured for bacteria, 43 of the fluids yielded bacteria, 40 of which were *Streptococcus pneumoniae*, *Haemophilus influenzae*, or β–hemolytic streptococcus. Only 1 (0.1 percent) of 858 cases of nonbullous otitis media was culture-positive for *M pneumoniae*. The erroneous assumption that bullous myringitis is pathognomonic for *M pneumoniae* infection began in 1962 after a study by Rifkind et al.[16] Fifty-two volunteers were inoculated with the Eaton agent, but only two cases of bullous myringitis were found in the 27 antibody-negative men and no cases in the 25 antibody-

positive men. Neither of the two cases had a positive culture for *M pneumoniae*.

Laboratory Diagnosis of *Mycoplasma pneumoniae* Pneumonia

Cold agglutinins (nonspecific, erythrocyte-agglutinating antibodies) are associated with *M pneumoniae* but are not specific for *M pneumoniae* infection. Cold agglutinins appear in only one half of those persons infected with the organism and are no longer considered an adequate means of diagnosis. False-positive cold agglutinin titers occur in patients with lymphoproliferative disorders, infectious mononucleosis, syphilis, influenza, adenovirus infection, and *Legionella pneumophila* infection.[17]

The complement fixation test (which detects both IgG and IgM) generally has replaced the cold agglutinin test. A fourfold rise in complement fixation titer during the acute and convalescent phases is diagnostic for *M pneumoniae* infections. The problem with the complement fixation test and most other serologic tests used in the laboratory diagnosis of *M pneumoniae* infection is the retrospective nature of the test as a result of the 10- to 14-day period required between obtaining acute and convalescent sera samples. Culture is another means of diagnosis; however, 5 to 20 days are required to grow *M pneumoniae*.

Recently an enzyme immunoassay[18] for *M pneumoniae*-specific IgM was found to be positive in as many as 80 percent of cases after 1 week of infection. IgM could be present from a previous infection, however, because antibody to *M pneumoniae* can remain elevated for as long as 4 years. It might be more helpful to observe a negative IgM (several days after the infection manifests itself) become positive 10 to 14 days later. In that *M pneumoniae*-specific IgG antibody levels can remain elevated for years after infection, antibody testing has not been useful in diagnosing acute infections.

A reference laboratory (Associated Regional University Professors, Salt Lake City, Utah) that tests samples from throughout the United States found that less than 10 percent of their tests for *M pneumoniae*-specific IgM are positive (Carl Schroder, MT(ASCP), written communication, 13 January 1997). This finding suggests that the incidence of *M pneumoniae* respiratory infection could have been overestimated by clinicians ordering the test. It is possible that the overestimation of the incidence of *M pneumoniae* infection could have been abetted by the marketing of commercially available diagnostic tests for detection of *M pneumoniae*. One manufacturer[19] of an *M pneumoniae*-specific IgM antibody test incorrectly states in the beginning of its test kit information sheet that "*Mycoplasma pneumoniae* is the most common cause of pneumonia and febrile upper respiratory tract infections in the general population (except for influenza A)." The previously mentioned studies by Gnarpe et al,[11] as well as the reference laboratory data, cast a great deal of doubt on that statement.

Other laboratory results that can assist in diagnosing *M pneumoniae* infection include complete blood cell counts, erythrocyte sedimentation rates, and chest radiographs. White cell counts in *M pneumoniae* infections exceed 10,000/μL in only 30 percent of the cases. Erythrocyte sedimentation rates can be markedly elevated. Chest radiographs usually show a unilateral segmental pneumonia, and three lobes are rarely involved. Pleural effusions have been noted in about 25 percent of the cases.[17] Twenty percent of patients have chest radiographic abnormalities for up to 4 months.

Summary

The incidence of *M pneumoniae* pneumonia has been reported to be as high as 51.7 percent in one population.[8] This report, however, was published 30 years ago and used throat cultures as a confirmatory diagnostic test. Another study widely quoted in the literature[7] concluded that the incidence of *M pneumoniae* pneumonia in community-acquired disease was 15 percent. Again, throat cultures were used in arriving at this statistic, and the work of Gnarpe et al[11] casts serious doubt on counting positive throat cultures as an indication of disease. Awareness of the common symptoms and judicious use of the complement fixation testing method could result in truer determinations of *M pneumoniae* infection incidence. We must be cautious in using rapid diagnostic tests that are not comparable with the reference standard of a fourfold rise in antibody titer.

M pneumoniae pneumonia is a disease that can occur in populations with close living or working conditions. The physician should suspect this disease when clusters of such illness are observed. Treating every pneumonia as a potential case of

M pneumoniae infection is not consistent with recently published facts about the illness, and it also increases the cost of health care. Medicine is an art, but it must be practiced with knowledge of the facts of science. Assumptions based on faulty data can lead to erroneous clinical decisions and constantly must be challenged if high-quality medicine is to be practiced.

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