the opportunity to interact and bring their special knowledge and abilities into an integrated game plan for the advantage of each patient.

This approach can result in improved care, possibly at diminished cost, by permitting the development of comprehensive, integrated, patient-specific treatment plans that cut across the different disciplines involved. A goal is to eliminate redundancy of treatment and thus avoid patient frustration and needless dissipation of funds. The team and center can function in a research and educational capacity by building a database of the success and failure of specific simple and complex treatment protocols applied to different classes of patients. The treatment of OSAS appears to have reached the level of complexity where the team approach might be considered.

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Severe Mycoplasma Disease—Rare or Underdiagnosed?

PNEUMONIA IS one of the most common causes of morbidity and mortality in all age groups, but particularly in the very young and the very old. Yet, the causal agent remains unidentified in as many as 50% of cases. *Mycoplasma pneumoniae* is among the smallest free-living microorganisms, being intermediate in size between bacteria and viruses.[1] Its small genome and small size cause diagnostic difficulties. The organism is not visible on Gram's stains and does not grow on standard bacteriologic media. Even on specialized media, it can require as long as two to three weeks for growth and positive identification. More rapid antigen detection assays and the detection of nucleic acid by polymerase chain reaction appear promising, but still require serologic proof of current infection. Thus, most clinical laboratories and physicians' offices do not have the capability to diagnose this infection on a routine basis.

Because of diagnostic difficulties, the diagnosis of *M pneumoniae* infection is often based on excluding other agents. This has resulted in our lack of understanding of the disease-producing potential of this organism and perhaps its underdiagnosis in various patient populations. Based on recent studies using multiple diagnostic techniques, our concept of *M pneumoniae* respiratory disease is changing. *M pneumoniae* was previously thought to occur primarily in persons 6 to 21 years of age. Consequently, *M pneumoniae* was often not considered in the differential diagnosis of pneumonia in other age groups. This organism was thought to cause only a mild respiratory disease, so that it was not considered in the differential diagnosis in persons with severe pneumonia, particularly those who were admitted to a hospital or those who died. Extrapulmonary manifestations were reported in association with *M pneumoniae* respiratory infection almost half a century ago, but because of diagnostic difficulties the etiologic importance of *M pneumoniae* in these conditions was doubted.

Based on cultural isolation directly from the affected site, in combination with one or more additional diagnostic tests, there can no longer be doubt that *M pneumoniae* causes pneumonia in all age groups that can be fatal and that in some persons this same organism has the ability to produce invasive infection resulting in protean clinical manifestations. The cases reviewed by Chan and Welsh elsewhere in this issue of the journal are good examples and emphasize the need for further studies of this common respiratory pathogen.[2]

Mycoplasma pneumoniae *as a Cause of Disease in All Age Groups*

Current evidence indicates an infection rate of about 20% to 30% per year for *M pneumoniae*. The incidence rate is highest among schoolchildren and second highest among children younger than 5 years.[3] This organism was previously thought to be rare among children younger than 5 years and was thought to cause only acute, self-limited respiratory tract disease. Recent studies indicate that the peak age incidence may actually be highest among 3- and 4-year-old children and that there is a high rate of admission to hospital for *M pneumoniae* pneumonia among children younger than 5.[3,4] The popular belief that *M pneumoniae* disease is rare in this age group has precluded physicians from even considering it in the differential diagnosis.

One of the most comprehensive studies of the cause of severe respiratory disease in children was done by Kok.[5] Bacterial, mycoplasmal, and viral cultures plus serologic studies were done on 1,600 children younger than 15 years who were admitted to a hospital with severe respiratory disease. Overall, 6% of the cases were culture-positive for *M pneumoniae*, and of these, more than half were younger than 5 years. Of all *M pneumoniae* organisms identified, 20% were from children younger than 1 year. Of patients in whom *M pneumoniae* was identified, 72% were suffering from pneumonia, whereas the remaining 28% (18 of 64) of isolates were from patients with croup, bronchiolitis, or upper respiratory tract symptoms. The reverse was the case for those with evidence of viral infection: 64% of these had croup, bronchiolitis, or bronchitis, with the rest having evidence of pneumonia. In a prospective study of children admitted to the hospital for radiologically confirmed community-acquired pneumonia in Finland,[6] *M pneumoniae* was found to be the causative agent in 20%.

Recent studies in patients with a mean age of 62 years indicate that *M pneumoniae* also accounts for as many as 15% of cases of community-acquired pneumonia in this age group.[7,8] Prospective studies of adults (mean age, 56 years) admitted to a hospital with community-acquired pneumonia have confirmed that as many as 18% of cases are caused by *M pneumoniae*.[9] Thus, current evidence indicates that *M pneumoniae* should be considered in the differential diagnosis of pneumonia in all age groups, including patients with more severe disease.

Fulminant Pneumonia

Although severe mycoplasmal respiratory disease has been thought to be uncommon, recent reports, including the cases summarized in this issue of the journal,[2] suggest that the disease spectrum is wider than previously thought and that severe pulmonary involvement can occur in otherwise healthy children and adults of all ages. Because of the failure to routinely include *M pneumoniae* in the differential diagnosis of fulminant pneumonia, the exact frequency with which it occurs is unknown. The severe disease, often mimicking necrotizing bacterial pneumonia, can initially cause diagnostic confusion and therapeutic anxiety. Lung abscesses, Swyer-James syndrome, pneumatoceles, extensive lobar consolidation, respiratory distress, and pleural effusion may occur.[10] Although pleural effusion was formerly thought to be so rare in mycoplasmal infection that it suggested a different diagnosis, small effusions can be demonstrated in at least 20% of patients with the use of lateral decubitus chest roentgenograms.[11,12] *Mycoplasma pneumoniae* can be isolated from the pleural fluid in more severe cases.[12,13] *M pneumoniae* has been associated with exacerbations of chronic respiratory disease, in particular, chronic bronchitis and asthma,[10] but the role of this organism in sustaining the chronic state or in initiating exacerbation is unknown. The proven role of mycoplasmas in similar chronic diseases of numerous animal species,[1] however, suggests that careful, systematic studies should be undertaken. As indicated in the cases summarized by Chan and Welsh, anecdotal evidence suggests that the administration of corticosteroids may be useful in the treatment of severe cases of *M pneumoniae* infection.[2] Controlled treatment trials are critically needed, however. Whereas pulmonary lesions may appear less severe in immunocompromised persons and in animals, disseminated mycoplasmal infections involving multiple organ systems are much more prone to develop in these persons.[14]

Extrapulmonary Complications

Although a number of nonpulmonary complications occur in association with *M pneumoniae* infection, their exact incidence, pathogenesis, and clinical spectrum are unknown.

Central nervous system (CNS) complications were described in the initial report of primary atypical pneumonia in 1938, but because the cause of the respiratory condition was not yet known to be *M pneumoniae*, little could be deduced regarding the relation between the two. In the years that followed, many additional reports appeared. Up until 1978 more than 87 cases had been described, and by 1981 an additional 50 had been reported.[10] Over the past decade, individual case reports continue to be published almost monthly. Yet, the precise incidence has not been determined. Meningoencephalitis, aseptic meningitis, brain-stem encephalitis, ascending paralysis (Guillain-Barré–like), and transverse myelitis have all been reported to occur as complications of *M pneumoniae* infection. Cerebral, cerebellar, spinal cord, and nerve root involvement have occurred in combination, resulting in acute psychosis, cerebellar ataxia, and cranial nerve palsies.

Recovery from neurologic dysfunction has often been slow, requiring many months of hospital care. Some cases have been fatal (overall mortality, 10.3%), and about a third of the patients who have recovered have been left with a permanent or persistent neurologic deficit. Two of the seven patients with fatal nonrespiratory failure reviewed in this journal by Chan and Welsh had CNS involvement (meningoencephalitis and brain

edema in one and cerebritis, meningitis, and cerebrovascular thrombi in the other).[2]

Initial failure to show direct CNS invasion by mycoplasmas and the fact that many reported cases were based solely on serologic evidence led many investigators to regard the association of *M pneumoniae* infection and CNS disease as rather tenuous. As stated by one investigator,[15] when a disease is as common as *M pneumoniae*, it can be related by coincidence alone to many life events. Several factors suggest that the association may be more than tenuous, however. It has been estimated that 0.1% of all patients with *M pneumoniae* infection and 7% of those requiring admission to a hospital have CNS complications.[12,16] On the other hand, the incidence of *M pneumoniae* infections among patients with acute, febrile, nonbacterial affection of the CNS was shown to be 5%, with a maximum of 10% during an epidemic.[17] These figures are supported by the fact that in five succeeding years, a constant percentage (6.7%) of patients with *M pneumoniae* infection were shown to have CNS complications.[18] More than half the reported patients with CNS disease have been from 6 to 21 years of age—the age group most prone to have *M pneumoniae* respiratory disease. Support is also afforded by the similar distribution, both seasonal and annual, of the patients with CNS symptoms and other manifestations associated with serologically verified *M pneumoniae* infection.[16]

The repeated occurrence of mycoplasmal pneumonia and encephalitis in immunocompetent persons suggests some as-yet-unexplained predisposition.[19] The absence of concomitant bacterial or viral pathogens was demonstrated in a number of patients with CNS disease,[15,20] whereas *M pneumoniae* infection was documented by a fourfold rise in the titer of complement-fixing antibody, the presence of typical respiratory symptoms, and the development of cold agglutinins. Diagnosing infection by a rise in complement-fixing antibody titer alone has been a cause for concern because the lipid antigen used in this test cross-reacts with certain lipid antigens in brain.[17] Findings in more than 1,000 patients with neurologic disease of other causes, however, suggest that nonspecific serologic cross-reactivity does not lead to an erroneous diagnosis of *M pneumoniae*-associated CNS disease.[12,18] More important, infection has been documented by cultural isolation of *M pneumoniae* from the cerebrospinal fluid and brain tissue at autopsy.[21-23] Thus, an association between CNS disease and *M pneumoniae* infection clearly exists, but further cultural and serologic studies are needed for a better understanding of their precise relation.

In 33% to 76% of patients, *M pneumoniae* infection evokes immunoglobulin M autoantibody that agglutinates human erythrocytes at 4°C (cold agglutinins). Positive Coombs' tests in 83% of patients and the presence of reticulocytosis in 61% suggest that subclinical anemia may be common.[11] Mycoplasmal organisms use specific long-chain sialo-oligosaccharides at the host cell surface as receptors. These sialo-oligosaccharides contain I antigen, and they are richly expressed at the primary site of infection—the ciliated bronchial epithelium—and on erythrocytes. The autoantibodies directed to I antigen, frequently produced in this infection, are antibodies to receptors and may be triggered by an autoimmunogenic mycoplasma-receptor complex in which the lipid-rich microorganism serves as an adjuvant.[24] Complications with or without the hemagglutination response include hemolytic anemia, paroxysmal cold hemoglobinuria, Raynaud's disease, peripheral symmetric gangrene, diffuse intravascular coagulation, thrombocytopenia, and renal failure.[11,16] Hemolytic anemia was a common finding in the fatal cases summarized by Chan and Welsh.[2]

Cardiac involvement in *M pneumoniae* infection is generally thought to be rare, but its actual incidence is unknown. The one prospective study reported shows that cardiac involvement may occur in as many as 4.5% of patients.[25] Myocardial dysfunction is often associated with hemolytic anemia and may mimic myocardial infarction.[26] Myopericarditis, hemopericardium, congestive heart failure, and complete block have been reported to occur.[12,16] The signs and symptoms of acute illness are variable, but may require intensive care with ventilatory assistance, temporary pacemakers, and defibrillation.[25] Cardiac sequelae have been known to persist for as long as 47 months.[27] In other patients, pronounced electrocardiographic changes reflecting myocarditis may be present without cardiac symptoms.[27] Myocarditis was present in several of the fulminant cases reviewed by Chan and Welsh.[2]

Although it is difficult to arrive at any definitive conclusions regarding cause and effect from published reports of myocardial involvement, the clinical presentations suggest an association with *M pneumoniae*. Cultures are negative for bacteria, and in most cases viral serologic tests are either negative or unchanged. *M pneumoniae* infection has been documented by a fourfold rise in antibody titer, elevated cold agglutinin levels, typical respiratory signs and symptoms, and direct isolation of *M pneumoniae* in pure culture from pericardial fluid and cardiac tissue.[11,28] In a prospective study of 57 patients with new, large pericardial effusions who underwent subxyphoid pericardiotomies, *M pneumoniae* was identified in pericardial tissue or fluid (or both) in 2.[29,30] No other cause of the pericarditis was identified in these two patients. Neither of the patients had pneumonia at the time, but one of them did have pleural effusion. Both were older than 60 years and had other underlying diseases.

Mucocutaneous lesions occur in approximately 25% of cases of serologically or culturally proved *M pneumoniae* infection.[11,12,31-33] Of these lesions, erythematous maculopapular and vesicular exanthems are most common. Half of these patients also have ulcerative stomatitis and conjunctivitis—Stevens-Johnson syndrome. Although the cause of this disease appears to be complex, more than 20 cases have been well documented to have *M pneumoniae* infection.[11,31,34,35] In addition to serologic evidence of infection, many patients have had

throat cultures positive for *M pneumoniae* and positive bullae-fluid cultures.[31,36] It has been suggested that *M pneumoniae* infection simply intensifies the dermatosensitive potential of certain antibiotics, but the development of the Stevens-Johnson syndrome in patients before therapy supports the contention that exanthems can occur in the absence of antibiotic therapy.[31,34] Other skin lesions that also occur in association with *M pneumoniae* infection but that are not of major importance include macular, petechial, morbilliform, and papulovesicular rashes; scaly erythema; pityriasis rosea; erythema nodosum; varicella-like rashes; and urticaria.[31]

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