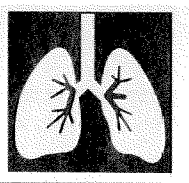

How to use what we know about *Chlamydia pneumoniae*

By David L. Hahn, MD

Chlamydia pneumoniae is a relatively newly identified pathogen. It is a common cause of nosocomial and community-acquired pneumonia and has been linked to a variety of other respiratory diseases. The infection is hard to diagnose because its clinical presentation is nonspecific and accurate laboratory studies are difficult to perform and unavailable in many areas. The author describes what is known about the pathogen's laboratory and clinical manifestations, and recommended treatment. Alert clinicians can help expand the knowledge of the organism's manifestations.

C pneumoniae was only recently recognized as being able to cause respiratory disease in humans.[1-3] One report estimates that the organism is responsible for several hundred thousand cases of pneumonia annually in the United States.[4] *C pneumoniae* has also been associated with wheezing, asthmatic bronchitis, asthma, pharyngitis, laryngitis, tonsillitis, and sinusitis.[5-10] It is not a new pathogen, however, and is well-established in human populations. Many seroprevalence studies have shown that antibodies to *C pneumoniae* are found in 40% to 60% of adults worldwide. Most infections with the organism are probably asymptomatic or only minimally symptomatic.[11] Because primary infection generates a transient antibody response, the high antibody prevalence suggests that reinfection or chronic infection is common.

Clinical manifestations

It is unlikely that the full clinical spectrum of disease caused by *C pneumoniae* is fully appreciated because laboratory testing for the organism is difficult and not widely available. It is already apparent that, although pneumonia is the most common of the illnesses known to be caused by the organism, many other respiratory diseases are linked to infection with this pathogen. Distinguishing *C pneumoniae* infection from viral or mycoplasmal illness on clinical grounds alone is difficult. Table 1 summarizes the illnesses currently associated with *C pneumoniae* infection in adults.

C pneumoniae has been reported as the etiologic agent in 6% to 12% of atypical pneumonia diagnosed in outpatient settings, as the cause of several epidemics of mild pneumonia in Scandinavia, and as a relatively frequent cause of community-acquired pneumonia requiring hospitalization.[8-10] It has been ranked as the third or fourth most commonly identified cause of pneumonia (6%) in hospitalized patients, below only *Streptococcus pneumoniae* and *Haemophilus pneumoniae* (and *Legionella* species in one study).[12,13] Pneumonia caused by *C pneumoniae* is usually mild, but deaths attributable to it have been reported in older adults with coexisting disease and in children in developing countries.

Lower respiratory tract illness produced

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TABLE 1

Clinical presentations of *C pneumoniae* infection

Often asymptomatic
Respiratory illness
Bronchitis, sometimes with wheezing
Pneumonia
Often accompanied by pharyngitis, laryngitis and/or sinusitis
Influenza-like illness
Case reports
Culture-negative endocarditis and myocarditis
Erythema nodosum
Otitis media with effusion
Conjunctivitis in a laboratory worker
Guillain-Barré syndrome following respiratory infection
Antibody associations
Adult-onset asthma
Sarcoidosis
Chronic obstructive pulmonary disease
Coronary artery disease

by *C pneumoniae* infection is often accompanied by pharyngitis, laryngitis, or sinusitis. The frequency of pharyngitis as the sole symptom of infection is variable, with one study reporting an incidence of less than 1%[5] and another finding a prevalence of 8.5%.[6] Tonsillitis has occasionally been reported. Approximately 5% of bronchitis in adults is due to *C pneumoniae* infection. The clinical presentation is generally indistinguishable from bronchitis due to infection by other organisms, such as *Mycoplasma pneumoniae* or viruses.[7]

In some cases, symptoms of upper respiratory infection precede clinical indicators of lower-respiratory illness, producing a "biphasic" presentation, but this pattern may not be predictive of *C pneumoniae infection* (Hahn DL: unpublished data). *C pneumoniae* may also produce an "influenza-like" picture of illness. Gradual onset of symptoms, abnormal breath sounds and hoarseness, and more relapse and persistence of clinical illness are clinical characteristics that have been statistically associated with *C pneumoniae* infection.[7,10] The positive predictive value of these indicators has not been adequately evaluated, and they are probably of little value for differentiating *C pneumoniae* from other causes of respiratory infection.

C pneumoniae antibody recently has been associated with wheezing, asthmatic bronchitis, and adult-onset asthma.[10] This has led to the suggestion that *C pneumoniae* infection could play a role in the increase in asthma noted in recent years,[14] but the precise clinical relevance of these findings is uncertain. Additionally, chronic obstructive pulmonary disease (COPD)[15] and sarcoidosis[16] have been associated with unusually high prevalence rates of *C pneumoniae* antibody. The clinical significance of these associations is unclear at this time.

C pneumoniae has been isolated from bronchoalveolar lavage fluid of patients with the acquired immune deficiency syndrome[17] and has been reported as the etiologic agent in an unusual case of multifocal bronchiolitis and pneumonia in an immunocompromised host.[18]

Conjunctivitis has only been reported in an inadvertantly infected laboratory worker who routinely handled chlamydial agents.[19] *C pneumoniae* infection should be included in the differential diagnoses of culture-negative endocarditis[20] and erythema nodosum.[21] A single case report has documented isolation of *C pneumoniae* from the middle ear aspirate of an adult with otitis media with effusion (OME).[22] Whether *C pneumoniae* infection plays a significant role in OME or in chronic sinusitis is unknown, but should be studied.

Laboratory diagnosis

Because of *C pneumoniae* infection's nonspecific clinical presentation, diagnosis depends heavily on laboratory confirmation of infection. The microimmunofluorescence (MIF) test, developed by Wang and Grayston initially for the study

of *C trachomatis*, is the most useful serologic test for *C pneumoniae* infection. This test can detect either IgM or IgG human antibody directed against *C pneumoniae*, although some laboratories use a polyvalent (IgG and IgM) antibody instead of IgG alone as a screening test. Testing for IgM is particularly important if antibiotic treatment has been given, because antibiotics appear to suppress the development of IgG, but not IgM, antibody.[21] It is always prudent to test for IgM antibody as well as for IgG (or polyvalent) antibody because in cases in which IgG or polyvalent antibody are present only in low titer, the presence of IgM antibody may be the sole criteria on which to base a serologic diagnosis of acute infection.

Currently accepted criteria for acute infection are any titer of IgM greater than or equal to 1:16, a four-fold rise in either IgM or IgG titer, or an IgG titer greater than or equal to 1:512, although this latter criterion is admittedly arbitrary. These serodiagnostic criteria are likely to be refined in the future.

The antigen in the current MIF test is the prototype TWAR strain, an organism originating from Taiwan. Until recently, the TWAR strain was believed to be the only strain of *C pneumoniae*. However, evidence has emerged that there may be other strains prevalent in different geographic regions.[23] This rather technical point may be clinically important because it is possible that *C pneumoniae* infection in some areas may be underdiagnosed by the current MIF test. The clinician who is interested in obtaining *C pneumoniae* serologic tests should ask his or her laboratory pathologist to recommend the nearest reputable laboratory that performs the MIF test. If MIF testing is unavailable in your area, I can provide instructions for obtaining *C pneumoniae* serologies.

Cell culture can also be used to identify infection with *C pneumoniae* but the technique requires a specialized laboratory able to maintain appropriate cell lines. The organism has been recovered from sputum, and from tonsillar and oropharyngeal swabs, but variable success rates in isolating the organism in serologically proven cases of infection suggest that there will be significant problems in obtaining adequately viable clinical samples that can be successfully cultured in routine practice. These barriers have led to the investigation of "rapid" tests for the diagnosis of *C pneumoniae* infection, which include various chlamydia immunoassay tests and a modification of the direct fluorescent assay test currently used for diagnosis of *Chlamydia trachomatis*. The most promising test, in theory at least, is the polymerase chain reaction test, which is currently being investigated for its ability to amplify even a few strands of *C pneumoniae*-specific DNA sequences. None of these direct tests are avalable for routine clinical use at this time.

Two other laboratory markers for infection are the erythrocyte sedimentation rate, which exceeds 15 mm/hr in about 75% of cases of confirmed significant illness, and the leukocyte count, which is usually normal.[7] Neither of these tests are likely to be useful in diagnosis, however.

Treatment

At this writing, there are no published treatment trials for *C pneumoniae* infection. Erythromycins (including the newly introduced macrolide agents, clarithromycin and azithromycin), tetracyclines, and some quinolones demonstrate in vitro activity against the organism, suggesting that these agents should be clinically efficacious. ß-lactam antibiotics (penicillins and amoxicillin, for example) decrease infectivity of *C pneumoniae* in vitro, but are not bactericidal; sulfas show neither activity against *C pneumoniae*.

Clinical experience shows that symptoms of *C pneumoniae* infection frequently relapse after short or conventional courses of appropriate antibiotics, such as 5 to 7 days of erythromycin or tetracycline. Therefore, treatment with higher doses for a longer time period is recommended: tetracycline 500 mg four times daily for 14 days, doxycycline 100 mg twice daily for 14 days, or erythromycin 500 mg four times daily for 14 days or 250 mg four times daily for 21 days have been recommended.[11] Relapse may occur even after these longer treatment courses, and these symptoms may respond to a second treatment course, preferably a tetracycline.

Conclusion

It is apparent that clinical diagnosis and laboratory identification of respiratory illness due to *C pneumoniae* infection is difficult at present because of its nonspecific clinical presentation and lack of

widespread availability of laboratory testing. The most practical advice that can be given to clinicians at this time is to consider inclusion of *C pneumoniae* coverage whenever antibiotics are indicated for significant respiratory illnesses that could be caused by *C pneumoniae*. Examples of illness that could involve *C pneumoniae* respiratory infection include any community-acquired atypical pneumonia or nosocomial pneumonia, and prolonged bronchitis, including respiratory infection that relapses after standard courses of therapy. Preliminary evidence also suggests that *C pneumoniae* infection may lead to prolonged reactive airways disease (adult-onset asthma) following bronchitis or atypical pneumonia, as well as wheezing exacerbations of COPD (Hahn DL: submitted for publication). However, the efficacy of prolonged courses of antichlamydial therapy in these conditions remains to be established. This recommendation is certainly subject to the criticism of nonspecificity because of the protean manifestations of *C pneumoniae* respiratory tract infection. It is likely that *C pneumoniae* infection is currently underdiagnosed. It is possible that new syndromes associated with infection by this pathogen have yet to be described, and that primary care clinicians, by alert application of current diagnostic techniques, may extend the clinical spectrum of disease known to be caused by the pathogen. **IM**

EDITOR'S NOTE

For help with obtaining serologic testing for *C pneumoniae*, readers can contact Dr. Hahn at (608) 246-2280.

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