Immunopathogenesis of Chlamydia pneumoniae Infections in Children

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Chlamydia pneumoniae is emerging as a frequent cause of respiratory disease in children as well as adults. C. pneumoniae infection in children presents a different set of problems regarding disease presentation and diagnosis compared to adults. Several studies of the role of C. pneumoniae in lower respiratory tract infection in pediatric populations have found evidence of infection in 0 to over 18%. Most of these studies have relied entirely on serology for diagnosis. Infection under the age of 5 years has been rare in Seattle and Scandinavia, whereas in a study of Filipino children under the age of 5 years presenting with lower respiratory tract infection, nearly 10% had either acute or chronic antibody to C. pneumoniae. In Brooklyn, the proportion of lower respiratory tract infections associated with C. pneumoniae, as determined by culture, increased from 9% in children under the age of 5 to 19% in the 5–16-year-old age category. Recent studies which have utilized culture have found a poor correlation between culture and serology, especially in children. As part of a multicenter pneumonia treatment study in children 3–12 years of age, Block et al. isolated C. pneumoniae from 34 of 260 (13.1%) of the children enrolled. Serologic evidence of acute infection was found in 48 (18.5%), but only 8 (23%) of the culture positive children met the serologic criteria for acute infection. The serologically positive culture negative children usually had stable high IgG titers, but no detectable IgM antibody. Most C. pneumoniae infections are probably mild or asymptomatic. Initial reports emphasized mild atypical pneumonia clinically resembling that associated with Mycoplasma pneumoniae. In several subsequent studies, however, pneumonia associated with C. pneumoniae has been clinically indistinguishable from other pneumonias. Coinfection with other pathogens, especially M. pneumoniae and Streptococcus pneumoniae can be frequent. In the multicenter pneumonia treatment study 20% of the children with positive C. pneumoniae cultures were coinfected with M. pneumoniae; they could not be distinguished from those children who were infected with either organism alone. The only child in this study who had pneumococcal bacteremia also was culture positive for C. pneumoniae. C. pneumoniae has been associated with severe illness and even death, although the role of pre-existing chronic conditions as contributing factors in many of these patients is difficult to assess. In some cases, however, C. pneumoniae appears to be clearly implicated as a serious pathogen even in the absence of underlying disease. C. pneumoniae was isolated from the respiratory tract and the pleural fluid of a previously healthy adolescent boy with severe pneumonia complicated by respiratory failure and pleural effusions.

The role of host factors remains to be determined. Although C. pneumoniae has been detected in bronchoalveolar lavage fluid from 10% of a group of patients with AIDS and pneumonia, its clinical role in these patients is uncertain because most were coinfected with other well-recognized pathogens such as Pneumocystis carinii and Mycobacterium tuberculosis. Gaydos et al., recently identified C. pneumoniae infection by polymerase chain reaction (PCR) in 11% of a group of immunocompromised adults with AIDS, malignancies, and other immune disorders including systemic lupus erythematosus, sarcoidosis,

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and common variable immunodeficiency. We isolated *C. pneumoniae* from 6 of 31 (19%) children with sickle cell disease presenting with episodes of acute chest syndrome. *C. pneumoniae* infection in these patients appeared to be associated with more severe hypoxia than infection with *M. pneumoniae*. *C. pneumoniae* appears to act as an inflammatory trigger for asthma. There are several reports of patients with culture-documented *C. pneumoniae* infection who developed significant bronchospasm. One patient was diagnosed as having asthmatic bronchitis and was receiving systemic and topical steroids. She did not improve until her chlamydial infection was treated. Hahn et al. reported an association between serologic evidence of acute *C. pneumoniae* infection and wheezing in adults seen for lower respiratory tract illness. However, they were able to isolate the organism from only 1 of 365 patients. As part of a study in children, we isolated *C. pneumoniae* from 13 of 118 (11%) children 5–15 years of age who were initially evaluated for either new or acute exacerbations of asthma. Treatment of the infection appeared to result in both clinical improvement and improvement in pulmonary function test scores in 75% of the infected children. As we observed with the children with community acquired pneumonia, only 5 of the children with confirmed infection had detectable IgG antibody to *C. pneumoniae*. One child who was noncompliant with his antibiotic therapy was culture-positive on five occasions over a 3-month period. During this time no anti-*C. pneumoniae* antibody was ever detected in his sera. We detected specific anti-*C. pneumoniae* IgE in 85.7% of the culture-positive asthmatics compared to 9% of children with *C. pneumoniae* pneumonia who were not wheezing. We were also able to detect anti-*C. pneumoniae* IgE in sera of 4 patients, 9–41 years of age, with cystic fibrosis and *C. pneumoniae* respiratory infection. This suggests that bronchial reactivity seen with *C. pneumoniae* infection may be IgE mediated. The potential of *C. pneumoniae* to cause prolonged, persistent infection, often for months, may produce chronic inflammation and trigger bronchospasm in susceptible individuals. Preliminary studies demonstrate that *C. pneumoniae* stimulates production of IL-6 in HEP-2 cells. IL-6 is a precursor for histamine release.

*C. pneumoniae* has been demonstrated to induce in vitro ciliostasis in ciliated bronchial epithelial cells. Animal studies also suggest that steroids can reactivate *C. pneumoniae* lung infection in mice. Hydrocortisone has been demonstrated to enhance the growth of *C. pneumoniae* in vitro. However, hydrocortisone did not interfere with the activity of various antibiotics suggesting that steroid treatment could be continued if the patients are on appropriate antibiotic treatment. Immune-mediated phenomena, including erythema nodosum and iritis, has also been described complicating *C. pneumoniae* infection.

As isolation of *C. pneumoniae* was difficult and initially limited, more emphasis was placed on serologic diagnosis. Grayston et al. originally proposed a set of criteria for serologic diagnosis of *C. pneumoniae* infection with the MIF test that is used by many laboratories and clinicians. For acute infection the patient should have a four-fold rise in IgG titer, a single IgM titer of 1:16 or greater, or a single IgG titer of 1:512 or higher. Past or pre-existing infection is defined as an IgG titer of 1:16 or higher but less than 1:512. In initial infection, the IgM response appears about 3 weeks after the onset of illness and the IgG response appears at 6–8 weeks. In reinfection, the IgM response may be absent and the IgG occurs earlier, within 1–2 weeks. Because of the relatively long period until the development of a serologic response in primary infection, the antibody response may be missed if convalescent sera are obtained too soon, i.e., earlier than 3 weeks after the onset of illness. Use of paired sera also only affords a retrospective diagnosis, which is of little help in terms of deciding how to treat the patient. The criteria for use of a single serum sample have not been correlated with the results of culture and are based mainly on data from adults. The antibody response in acute infection may take longer than 3 months to develop. As discussed previously, acute, culture-documented infection can also occur without seroconversion, especially in children. Only 28% of the culture-positive children enrolled in the multicenter pneumonia treatment study had met the serologic criteria for acute infection; most had no detectable antibody by the MIF test even after 3 months of follow-up.

Subsequently, we tested sera from 46 culture positive children and 42 culture negative children with pneumonia or asthma by immunoblotting. Over 80% of the culture positive, MIF negative children had antibodies to a number of *C. pneumoniae* proteins detected by immunoblot. The lack of detectable antibody by MIF in these children may be due, in part,
to low reactivity to the major outer membrane protein (MOMP); only 23%–26% reacted with the MOMP. Although the MOMP has been demonstrated to be immunodominant in the immune response to *C. trachomatis* infection, and antibody to the MOMP is neutralizing, it does not appear to be so for *C. pneumoniae*. Over 75% of the culture positive children reacted with a 50–52 kDa protein compared to only 43% of the culture negative children. This protein may be a heat shock protein which is probably genus-specific. However, we could not determine any specific pattern in terms of reactivity to various *C. pneumoniae* proteins in sera from culture positive and culture negative children, even with paired sera. Possible serologic cross-reactions of *C. pneumoniae* with *C. trachomatis* and other bacteria may also occur and should be investigated.

**REFERENCES**


