

Review article

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Chlamydia pneumoniae, asthma, and COPD: what is the evidence?

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Learning objectives: Reading this article will familiarize the reader with (1) the unique chlamydial intracellular life cycle and the propensity for human chlamydial infections to become persistent and to result in immunopathologic (inflammatory) damage in target organs and (2) current evidence linking *Chlamydia pneumoniae* (*Cpn*) infection to obstructive lung diseases (asthma and chronic obstructive pulmonary disease, COPD). Potential therapeutic implications of the *Cpn*-asthma association are also discussed.

Data sources: All Medline articles (January 1985 to March 1999) that cross-referenced the exploded MESH headings "lung diseases, obstructive" and "*Chlamydia pneumoniae*" (N = 76). Additional referenced articles, published abstracts, book chapters, and conference proceedings were also utilized.

Study selection: (1) Case reports and case series that identified *Cpn* infection in asthma and/or COPD and (2) epidemiologic studies of markers for *Cpn* infection in asthma and/or COPD that included one or more control groups.

Results: Of 18 controlled epidemiologic studies (over 4000 cases/controls), 15 found significant associations between *Cpn* infection and asthma using organism detection (polymerase chain reaction (PCR) testing (n = 2 studies) or fluorescent antigen testing (n = 1)), *Cpn*-specific secretory IgA (sIgA) antibody testing (n = 1), and/or specific serum IgE (n = 2), IgA (n = 4), IgG (n = 3) or other antibody criteria (n = 7). Eight case reports and 13 case series of *Cpn* infection in asthma (over 100 patients) also include descriptions of improvement or complete disappearance of asthma symptoms after prolonged antibiotic therapy directed against *Cpn*. Significant associations with COPD (over 1000 cases/controls) were reported in 5 of 6 studies. Results of treating chronic chlamydial infections in COPD patients have not been reported.

Conclusions: Although the full clinical significance of these *Cpn*-obstructive lung disease associations remains to be established, reports of asthma improvement after treatment of *Cpn* infection deserve further investigation. Clinicians who manage asthma should be aware of this information since it may help to manage difficult cases. The hypothesis that *Cpn* infection in COPD can amplify smoking-associated inflammation and worsen fixed obstruction also deserves further study.

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INTRODUCTION

Chlamydia pneumoniae (*Cpn*) is an obligate intracellular human pathogen

that is an established cause for acute upper and lower respiratory tract illnesses including pharyngitis, sinusitis, about 5% of bronchitis and 10% to 15% of community-acquired pneumonia.¹ *Chlamydia pneumoniae* infection has also been associated with asthma and chronic obstructive pulmonary disease (COPD).^{2,3} The associations with

obstructive airway diseases raise intriguing questions regarding causation that have not yet been answered. Clinicians should be aware of existing information that might aid them in the management of difficult asthma patients in whom treatable infection could be a contributing factor.

BACKGROUND

Decades ago, many clinicians believed that infection played a key role in asthma etiology.⁴⁻⁶ Currently, expert opinion favors the concept that asthma is a noninfectious condition whose root cause is inflammation.⁷ Nevertheless, many unexplained aspects of asthma epidemiology, including increasing worldwide prevalence, might be related to the existence of infectious causes for asthma.⁸ In addition to an acknowledged role for acute viral infection in asthma exacerbations, there is growing interest in the possibility that viral infections (particularly RSV) during crucial time periods in immune system development could initiate asthma in susceptible individuals.⁹

Recent reports of persistent adenoviral¹⁰ and atypical¹¹ infections detected in asthma patients have also raised the possibility that infection could play a role in producing chronic asthma symptoms (asthma promotion). Reports that antibiotic treatment can improve symptoms and pulmonary function in persistent moderate^{12,13} and severe steroid-dependent¹⁴ asthma suggest that atypical infection may be clinically relevant. Evidence for such infection is most well developed for *Chlamydia pneumoniae*.² Acute infection with this organism can initiate¹⁵

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and exacerbate¹⁶ asthma and persistent infection may contribute to chronic asthma symptoms in some patients.¹³ The purposes of this CME review article are, first, to familiarize the reader with selected aspects of chlamydial pathophysiology, diagnosis and treatment and, second, to review the current evidence associating *Cpn* with asthma and COPD.

CHLAMYDIA: LIFE CYCLE AND IMMUNOPATHOGENESIS

Knowledge of the unique chlamydial life cycle and the propensity for chlamydial infection to become persistent and to produce immunopathologic damage in target organs is crucial to understanding potential pathophysiologic mechanisms that may apply to asthma and COPD. Four species of *Chlamydiae* (*C. psittaci*, *C. trachomatis*, *C. pneumoniae*, and *C. pecorum*) have been described; the first three cause human disease. *Chlamydia psittaci* infects multiple bird species and occasionally causes fulminant human pneumonia (psittacosis). *Chlamydia trachomatis* is a leading cause of preventable blindness (trachoma) and also produces neonatal conjunctivitis and pneumonia, adult inclusion blenorrhea and genitourinary infections whose chronic sequelae include ectopic pregnancy and tubal infertility. *Chlamydia pneumoniae* is a recently described human respiratory pathogen that is now acknowledged as an important cause for a variety of acute upper and lower respiratory tract illnesses including otitis, sinusitis, pharyngitis, bronchitis, and pneumonia.

Life Cycle

Once considered as unusual viruses because their life-cycle included an obligate intracellular stage, organisms belonging to the genus *Chlamydia* are now known to be obligate intracellular procarions sharing a unique reproductive life-cycle that includes: (1) a metabolically inert but cultivable extracellular electron-dense form termed the elementary body (EB), (2) attachment of the EB to a host (target) cell, (3) cell entry via endocytosis, (4) intracellular

survival via inhibition of endolysosomal fusion, (5) initiation of EB maturation and transformation into the metabolically active but non-cultivable intracellular energy parasite reticulate body (RB), (6) differentiation of new EBs from RBs and (7) completion of the life cycle by release of EBs via exocytosis or cell rupture.¹⁷

In vitro, the chlamydial life cycle (including host cell death) is completed within 3 to 4 days, implying a massive, overwhelming infection in vivo in the absence of host response mechanisms that limit replication. Since human chlamydial infections are generally persistent and of low severity, the host response to inhibit the chlamydial life cycle must be significant.¹⁸ Although both humoral and cellular immunity are mounted in response to chlamydial infections,¹⁹ chlamydiae appear so well adapted to intracellular life within humans that the host immune response does not appear always capable of eradicating the organism: the host response can be protective by limiting chlamydial reproduction but can also be damaging to the host by producing inflammation in infected tissues such as the eye (trachoma) or the genital tract (pelvic inflammatory disease and tubal infertility).¹⁸

Chlamydial Persistence

An in vitro model of chlamydial persistence has been developed²⁰ that has the following characteristics: (1) under the influence of interferon-gamma (IFN-g) the chlamydial RB fails to reproduce EBs but instead develops an atypical RB morphology; (2) chlamydial structural components including major outer membrane protein (MOMP) and lipopolysaccharide (LPS) are downregulated within these atypical RBs, whereas stress response proteins, particularly chlamydial heat shock protein-60 (chsp-60), are present in increased quantities; and (3) after removal of the inhibitory influence of IFN-g the normal life cycle resumes with the production of infectious EBs. Chlamydial persistence is related to intracellular amino acid deficiency.²¹ Furthermore, atypical RBs resembling those seen in the in

vitro persistence model can be induced by beta-lactam antibiotics that inhibit EB formation and cultivability but do not prevent the persistence of atypically large but viable RBs.²²

Immunopathogenesis

This in vitro model for chlamydial persistence has certain characteristics in common with the in vivo human diseases trachoma and tubal infertility: both diseases are associated with evidence of non-cultivable chlamydiae^{23,24} and with an immune response against chsp-60 that may contribute to the scarring chronic inflammatory damage that causes blindness in trachoma and tubal infertility following pelvic inflammatory disease.^{25,26} For these chlamydial diseases as well as for other intracellular parasitic infections, evidence suggests that (1) a vigorous Th1 response is required to control and/or eradicate the infection, (2) a predominantly Th2 response favors persistent infection leading to scarring sequelae, and (3) the Th1/Th2 balance may be genetically regulated.²⁷

It remains to be seen whether similar pathogenic mechanisms are operative in human organs, such as the lung and the vascular bed, within which *Chlamydia pneumoniae* has been shown to persist.^{28,29} In vitro evidence supports the existence of IFN-g-induced persistence of *Cpn*.²¹ Enhanced IFN-g production has been reported in human *Cpn* respiratory infection.³⁰ Both in vitro and in vivo data suggest that chsp-60 produced by deep tissue *Cpn* infection is biologically active to produce chronic inflammatory disease in humans.³¹

PATHOPHYSIOLOGY OF *Chlamydia pneumoniae*

It is becoming increasingly clear that *Chlamydia pneumoniae* infection, rather than resembling typical respiratory pyogenic infection, is more reminiscent of *Mycobacterium tuberculosis* infection that is characterized by opportunistic infection, intracellular persistence, dissemination, and reactivation.³² This paradigm is supported by a variety of animal experiments and hu-

man studies. Whether the analogy extends to the need for multiple antimicrobial agents to eradicate persistent *Cpn* infection remains unclear.

Animal experiments

Primary Lung Infection

After intranasal inoculation of previously unexposed mice, *Cpn* causes a primary infection pneumonia characterized by initial focal inflammation with neutrophils and macrophages in alveolar spaces,³³ extensive deceleration³⁴ and a later persisting mononuclear infiltrate at a time when culture of the organism is difficult, suggesting an immunopathologic basis for the acute phase of disease.³⁴ Despite difficulty in culture isolation, chlamydial inclusions can nevertheless be detected in primary infection pneumonia in broncho-epithelial cells, alveolar-epithelial cells and macrophages.^{34,35}

Secondary Lung (re)Infection

Intranasal inoculation of previously exposed mice produces a reinfection pneumonia characterized by bronchus-associated and perivascular accumulations of lymphoid and plasma cells.^{33,36} Compared with primary infection pneumonia, the number of inclusion bodies in reinfection is fewer³³ and the organism is non-cultivable.³⁶ Despite the relative paucity of organisms detected and lack of culture positivity in reinfection pneumonia, the inflammatory reaction is profound and rapid, further substantiating the likelihood of an immunopathologic reaction.³⁶ After administration of hydrocortisone, *Cpn* can again be recovered by culture, suggesting that viable but noncultivable *Cpn* organisms persist in the experimental pneumonia model.³⁷

Presence of antichlamydial IgG antibody (either natural or administered) is also associated with decreased organism recovery but does not change the severity of inflammation, suggesting that antibody may attack extracellular EBs but intracellular RBs may be protected from antibody neutralization.³⁸

Systemic Dissemination

Infection of lung macrophages can set the stage for systemic dissemination in animal models.³⁴ After intranasal inoculation in mice, *Cpn* is detectable in alveolar macrophages and peripheral blood mononuclear cells (PBMCs)³⁹ and can be consistently isolated from the spleen.³⁴ Furthermore, after adoptive transfer of infected alveolar macrophages by intraperitoneal injection into previously unexposed mice, *Cpn* can be detected in their lung tissue, thymus, spleen, and/or abdominal lymph nodes.³⁹ After primary lung infection via intranasal inoculation, rabbits also develop dissemination to PBMCs and spleen.⁴⁰ *Chlamydia pneumoniae* also invades the vascular endothelium in the rabbit model.^{41,42}

Human Studies

As in animal models, human respiratory infection by *Cpn* is characterized by persistence and systemic dissemination. Acute and chronic *Cpn* respiratory infections can also influence the severity of coexisting lung disorders.

Persistence

Persistent *Cpn* culture isolation has been reported following acute respiratory illnesses²⁸ and after antibiotic treatment resulting in clinical improvement. *Chlamydia pneumoniae* post-treatment persistence rates range from 13%⁴³ to 56%.⁴⁴ It is very common for *Mycoplasma pneumoniae* to be isolated from sputum or the upper respiratory tract for several weeks to several months after recovery from clinical illness.⁴⁵ *Chlamydia pneumoniae* has been detected in some patients' respiratory secretions for up to 2½ years.⁴⁶ Persistent culture positivity has also been reported during development of chronic asthma in adults.¹⁵ Evidence for persistent lung infection in alveolar epithelial and multinucleated giant (Langhans) cells in a COPD patient has also been reported (Hahn DL, Kuo C-C, Campbell LA, unpublished: presented at the World Asthma Meetings, Barcelona, Spain, January 1998).

Dissemination

There is now considerable evidence that *Cpn* resides in human deep tissues, since this organism is consistently detectable in atheroma lesions of patients with atherosclerosis.²⁹ The organism probably disseminates from the lung via intracellular infection of macrophage/monocytes following asymptomatic, acute and/or chronic respiratory infections. *Chlamydia pneumoniae* readily induces productive infection in human alveolar macrophages (AM) both in vitro^{47,48} and in vivo.⁴⁸ Evidence for the organism within circulating PBMCs has been reported in 59% of adults with atherosclerotic coronary artery disease and also in 46% of healthy blood donors.⁴⁹ Reports of *Cpn* infection associated with myocarditis,⁵⁰ reactive arthritis,⁵¹ and inflammatory nervous system diseases^{52,53} suggest that this organism may also disseminate to other tissues as a disease agent.

Promotion of Coexisting Lung Disorders

When *Cpn* is detected in community-acquired pneumonia (CAP), coinfection with other pathogens (particularly *M. pneumoniae* and *S. pneumoniae*) is a common feature.⁵⁴ When *Cpn* and *S. pneumoniae* infection coexist in CAP, the pneumonia is more severe than when *S. pneumoniae* is the sole infecting agent.⁵⁵ Chronic *Cpn* infection in chronic bronchitis (CB) increases the risk of bacterial colonization in CB.⁵⁶ Furthermore, the presence of *Cpn* infection in CB is associated with a decreased probability of bacteriologic eradication in acute bacterial exacerbations of CB.⁵⁷ The presence of *Cpn* infection in both acute and chronic lung diseases can thus act as a cofactor to promote clinical severity and/or poor therapeutic outcomes.

Potential Role in Asthma Pathogenesis

The pathogenesis of virus-associated asthma exacerbations has been postulated to involve several mechanisms

including epithelial damage, release of inflammatory mediators, and generation of virus-specific IgE antibodies.⁵⁸ Current evidence associating *Cpn* with asthma is insufficient to prove causality. Nevertheless, some mechanisms postulated for viral-associated asthma also apply to chlamydia-associated asthma: (1) *Cpn* infects the human bronchial tree causing ciliary dysfunction⁵⁹ and epithelial damage;⁶⁰ (2) chlamydia species, including *Cpn*, generate inflammatory cytokines both in vitro and in vivo;^{48,61} (3) *Cpn*-specific IgE has been associated with asthma in culture-positive children⁶² and has also been detected in patients with adult-onset asthma.⁶³ On the other hand, a recent study found that *Cpn*-specific IgE antibody, while very prevalent (69%) in adult asthma patients, was equally common in controls and *Cpn* could neither induce nor enhance histamine release from basophil leukocytes of patients or controls.⁶⁴

As discussed previously, chlamydial heat shock protein 60 (chsp-60) is important in the pathogenesis of established human chlamydial diseases including trachoma and tubal infertility. Two recent studies found associations between chsp-60 and asthma. Human immune response to chsp-60 was associated with "infectious" asthma (asthma symptoms beginning after an acute respiratory illness) in one study⁶³ and with both asthma and the degree of pulmonary obstruction in patients from another study⁶⁵ (Hahn, Huittinen and Saikku, unpublished data). These preliminary observations and others⁶⁶ suggest that host response against heat shock proteins may be important in asthma and should be investigated further.

Additional potential mechanisms include macrophage and/or smooth muscle dysregulation by *Cpn* and the ability of chlamydial lipopolysaccharide (LPS) to induce bronchial hyperreactivity. *Chlamydia pneumoniae* readily induces productive infection in the human AM^{47,48} which responds to infection with a marked dose-dependent release of reactive oxygen species, TNF-alpha, IL-1beta and IL-8 that may amplify local inflammatory responses

but is unable to prevent chlamydial infection.⁴⁸ In an animal model, intact AM function is required to downregulate the atopic response⁶⁷; thus, AM dysregulation by *Cpn* infection could hypothetically promote allergic sensitization to a wide variety of aeroallergens. *Chlamydia pneumoniae* also infects human smooth muscle cells⁶⁸ which could, again hypothetically, lead to smooth muscle cell dysregulation resulting in hyperresponsiveness. *Chlamydia pneumoniae* contains LPS related to gram negative bacterial LPS that (1) produces bronchial hyperreactivity in susceptible individuals⁶⁹ and (2) augments IgE responses to allergen.⁷⁰ Whether these hypothetical mechanisms have any relevance to asthma is unknown at the present time.

DIAGNOSIS AND THERAPY

For the clinician, diagnosis of *Cpn* infection is currently difficult because of (1) lack of widespread availability of diagnostic facilities for organism identification and serologic testing and (2) controversies surrounding serodiagnostic criteria. This section reviews some of the diagnostic techniques and their interpretation, with special emphasis on current limitations of chronic infection diagnosis.

Organism detection

Culture

Isolation of *Cpn* requires cell culture techniques that are currently available mainly in research settings and reference laboratories. The optimal cell line for culture isolation remains uncertain. *Cpn* grows less well in McCoy cells⁷¹ (the traditional cell line used for culture of *C. trachomatis*) than in HeLa cells⁷² and grows even better in HL cells⁷³ and Hep-2 cells.⁷⁴ Organism viability degrades rapidly if clinical specimens are stored or transported at room temperature for 24 hours. It has been recommended that specimens be stored at 4 degrees centigrade if isolation can be done within 24 hours, otherwise at <-70 degrees after 1 to 4 hours at 4 degrees if isolation cannot be done within 24 hours.⁷⁵ The lability

of *Cpn* at room temperature is probably related to low yields of positive culture isolation at some reference laboratories that depend on clinical specimens received in the mails; at least one of these laboratories has discontinued offering *Cpn* culture.

A comprehensive review of culture methods may be found elsewhere.⁷⁶

PCR

Polymerase chain reaction (PCR) testing has the advantage over culture that organisms rendered nonviable during shipping can remain detectable by PCR.⁷⁷ An additional advantage is that PCR detects noncultivable organisms in persistent infection.⁷⁸ A potential disadvantage is that DNA PCR techniques cannot distinguish viable from dead organisms after antibiotic treatment. Reverse transcriptase-PCR to detect messenger-RNA can indicate metabolic activity, however.⁷⁹ Polymerase chain reaction is more sensitive than culture of *Cpn*⁸⁰⁻⁸² but inter-laboratory standardization of PCR techniques is currently lacking and should be done before PCR is applied to widespread diagnosis in clinical settings.

Some culture and/or PCR studies of acute respiratory illnesses have reported a hierarchy of *Cpn* diagnostic yield from various specimen sites (sputum > throat swab > nasopharyngeal swab).^{81,83} Gargled water specimens have also been used to detect *Cpn*.⁸⁴

Immunocytochemical (ICC) staining of fresh and/or formalin-fixed, paraffin-embedded tissues, using either genus-specific or species-specific monoclonal antibodies, has been used to detect chronic *Cpn* tissue infection in upper respiratory⁷⁸ and cardiovascular diseases.⁸⁵

Serologic Methods

A single positive organism detection does not distinguish acute from persistent infection. To make this distinction, serologic responses must be evaluated in the context of the clinical condition being evaluated.

Microimmunofluorescence (MIF) Testing

The most widely used method for serologic testing employs an indirect im-

munofluorescence test using whole *Cpn* EB as antigen.⁸⁶ In general, only minor differences in antigenic reactivity have been found when EBs from different *Cpn* isolates have been used.⁸⁷ Proper interpretation of the MIF test requires technical expertise and a trained observer. When properly interpreted, the MIF test is the most sensitive and specific serologic test available for *Cpn*.⁸⁸ *Chlamydia pneumoniae* EBs display antigenic epitopes that cross react with antibodies against other chlamydia species and Bartonella. A trained observer can recognize cross reacting fluorescence which can be controlled for additionally by (1) treatment of EBs to eliminate genus-specific LPS and (2) simultaneous determination of MIF seroreactivity against cross reacting species. A limitation of this test in actual practice is that agreement between experienced laboratories when interpreting "gold standards" is good (80% agreement) but not perfect.⁸⁹ The best agreement (87%) has been for 4-fold rises in IgG titer.⁸⁹

Other Serologic Tests

The genus-specific chlamydial complement fixation (CF) test, traditionally used for diagnosis of *C. psittaci* infection (psittacosis), will also be positive in acute primary *Cpn* infections but is insensitive for detection of reinfections that are common in adults. Because most acute chlamydial respiratory illnesses are due to *Cpn*, several outbreaks of "psittacosis" diagnosed by the CF test were later proven to be caused by *Cpn*.^{90,91}

Immune complexes (IgM or IgG antibodies and chlamydial LPS or protein antigens) have been measured in specialized research settings.⁹² The persistent detection of chlamydial LPS immune complexes suggests nonlocalized chronic infection since LPS may diffuse into the circulation from elsewhere. Detection of (nondiffusible) chlamydial protein immune complexes implies infection localized to the circulatory system.⁹³ Persistent detection of *Cpn*-specific serum IgA (MIF test) and/or secretory IgA (ELISA) in respiratory secretions likewise suggest

chronic (mucosal) infection since the half-life of IgA is only 1 week.⁹⁴

A more comprehensive review of *Cpn* serologic techniques may be found elsewhere.⁹³

Serodiagnostic Criteria

The MIF test has proven extremely valuable in delineating the epidemiology and clinical importance of *Cpn*.⁹⁵ In the clinical setting, serodiagnosis using the MIF test is probably the most widely applied method. As with all diagnostic testing, some limitations of the MIF test must be acknowledged and understood.

Acute Infection

Standard serodiagnostic criteria for acute infection are: (1) A 4-fold or greater rise in IgM and/or IgG MIF antibody titer in paired sera obtained at least 4 weeks apart (IgA has also been included by some investigators), or (2) a single titer of IgM \geq 1:16 or (3) a single titer of IgG \geq 1:512.⁹⁶ IgM is present in acute primary infection and absent in acute secondary (re)infection.⁹⁷ A 4-fold antibody titer rise is unanimously regarded as definite evidence for acute infection whereas a single titer of IgM, or of IgG \geq 1:512, are regarded by some authorities as possible evidence for acute infection.⁹⁸

Seronegativity is defined as IgG and IgM MIF titers of $<$ 1:16. "Pre-existing" antibody, indicative of previous exposure, is defined as an IgG titer between 1:16 and 1:256 in the absence of IgM.⁹⁶ Persistent titers of "pre-existing" antibody have also occasionally been referred to as "chronic" antibody. While titers of this magnitude are often found in patients with proven persistent infection, it is not possible to distinguish previous exposure from persistent infection solely on the basis of serology. Confirmation by persistent organism detection is required but this is often difficult, particularly in deep tissue (eg, lung and cardiovascular system) infections.

In adult patient groups without underlying chronic cardiopulmonary diseases, the serodiagnostic criteria for acute infection (including criterion #3)

have shown excellent agreement with organism detection (culture isolation or PCR) in acute endemic^{72,99,100} and epidemic^{81,101,102} respiratory illnesses. The serodiagnostic criteria for acute infection have also shown good agreement with organism detection in two small studies of Japanese children with endemic¹⁰³ and epidemic¹⁰⁴ respiratory tract illnesses. Two large, multisite American studies of childhood pneumonia, on the other hand, found that a significant proportion of culture positive children did not meet serodiagnostic criteria for acute infection.^{43,105}

Reasons for the discrepancy between organism detection and an acute serologic response in these studies of children with pneumonia are not completely understood presently but probably involve complex interactions between the organism and an evolving host immune response during childhood. By early adulthood, at least half of general populations worldwide have been infected and have seroconverted.¹⁰⁶ Lack of MIF seroreactivity reported in some persistently culture positive children¹⁰⁷ may be related to prior antibiotic administration¹⁰² or to delayed antibody development that has also been observed in some children followed longitudinally (H. Gnarpe, personal communication).

Serologic findings must be interpreted cautiously in assessing patients with underlying chronic cardiopulmonary disorders that could be related to persistent *Cpn* infection.¹⁰⁸ Thus, reports that the serodiagnostic criteria for acute infection are insensitive in culture-positive children with acute exacerbations of asthma¹⁰⁹ could be due to pre-existing persistent *Cpn* infection (associated with chronic asthma) and superimposed acute viral infection (causing the acute exacerbation).¹¹⁰ In this scenario, persistent levels of "pre-existing" or "chronic" antibody, not acute antibody, would be expected.

Criterion (3) has been questioned because some asymptomatic members of the general population exhibit titers of this magnitude (\geq 1:512). Such titers could reflect a chronic nonpulmonary source of infection.⁴⁹ It is possible

Table 1. *Chlamydia pneumoniae* (*Cpn*) Infection and Asthma: Case Reports

Reference	Population from which Case Report Is Derived	<i>Cpn</i> Diagnostic Findings	Clinical Findings
Grayston et al 1986 ⁷²	13 University Health Service patients with acute <i>Cpn</i> respiratory infections	Positive culture, smear, and MIF* confirming an acute primary (first exposure) infection	35-year-old man with CAP† who never completely returned to normal after treatment with 1 gram per day of erythromycin for 5 days (for presumed <i>Mycoplasma pneumoniae</i> infection) and had a few expiratory wheezes on auscultation.
Frydén et al 1989 ⁹¹	16 Swedish patients with <i>Cpn</i> infection	Positive MIF	In one patient the disease initiated severe chronic asthmatic bronchitis.
Hammerschlag et al 1992 ²⁸	5 health care personnel with persistent <i>Cpn</i> infection	Persistent positive cultures	A 38-year-old female physician developed asthmatic bronchitis.
Kawane 1993 ¹¹⁹	A patient with cough variant asthma, bronchial hyperreactivity, eosinophilia and elevated IgE	MIF <i>Cpn</i> IgG = 1:1024, IgA = 1:32	Macrolide treatment was successful.
Hahn 1994 ¹²⁰	Adult primary care practice	Positive cultures ×3 and stable IgG titers = 1:128	35-year-old male with asthma and eosinophilia; asthma symptoms and eosinophilia disappeared, pulmonary function normalized, and patient became culture-negative after prolonged antibiotic treatment.
Thom et al 1994 ¹²¹	21 middle-aged and older outpatients with acute <i>Cpn</i> respiratory illnesses	Positive MIF and culture	One patient had persistent symptoms of new reactive airways disease.
Thom 1994 ¹²²	3 students with acute <i>Cpn</i> respiratory illnesses	Positive MIF (primary infection) and PCR‡ test	21-year-old female undergraduate diagnosed with sinusitis, pneumonia, and bronchospasm.
Aldous et al 1996 ¹²³	56 Tanzanian children with respiratory (31) or nonrespiratory (25) illness, aged 0–14 years	Positive MIF (2)	An MIF-positive 4-year-old boy had fever and bronchospasm.
Normann et al ¹²⁴	Swedish pediatric population with acute respiratory illness or acute episode of wheezing	Positive PCR‡ ×3, MIF IgG 4-fold titer increases	A 4-year-old boy with moderate asthma and several exacerbations associated with PCR positivity and 4× titer changes. After a second course of azithromycin he improved and was PCR negative.

* Microimmunofluorescence test.

† Community-acquired pneumonia.

‡ Polymerase chain reaction.

Table 2. *Chlamydia pneumoniae* (*Cpn*) Infection and Asthma: Case Series

Reference	Population from which Case Series Derived	<i>Cpn</i> Diagnostic Findings	Clinical Findings
Hahn et al 1991 ⁷¹	365 adult outpatients with acute respiratory illnesses	Positive MIF* (19) & positive culture (1/19)	9 patients had wheezing during acute illness; 4 had exacerbation of previous asthma & 4 others had newly diagnosed asthma after illness.
Korppi et al 1991 ¹²⁷	188 hospitalized children less than 6 years old with expiratory difficulty	Positive EIA† for <i>Chlamydia</i> genus antibody (8), <i>C. trachomatis</i> -specific MIF (0)	8 patients with expiratory difficulty seroconverted by EIA, specific tests for <i>C. trachomatis</i> were negative.
Hahn et al 1994 ¹²⁸	12 adults with asthma	Acute MIF antibody (2) Acute <i>M. pneumoniae</i> antibody (1)	1 patient with acute <i>Cpn</i> infection rapidly developed severe, steroid-dependent asthma; the second had persistent asthma symptoms and COPD.‡
Allegra et al 1994 ¹⁶	74 adult outpatients with an acute asthma exacerbation	MIF seroconversion (7)	3 primary & 4 secondary <i>Cpn</i> infections, 2 of these had a positive pharyngeal swab.
Emre et al 1994 ¹²	118 children with acute episodes of wheezing aged 5–16 years	Culture positive (13), MIF seroconversion (3/13)	9/12 culture positive children had clinical and laboratory improvement in asthma after microbiologic eradication; one child wheezed for the first time. Of 7 persistently culture-positive patients, only 1 seroconverted.
Prückl et al 1995 ⁸⁴	193 children with acute or chronic respiratory infections, aged 5–16 years	PCR§ positive on gargled water specimens (3)	All 3 had chronic obstructive bronchitis which had proved resistant to antimicrobial therapy.
Resta et al 1995 ¹²⁹	91 adults with respiratory infections	Serologic evidence of recent infection (13)	3 had asthmatic bronchitis, 5 had exacerbations of COPD.
Korppi et al 1995 ¹³⁰	449 children with lower respiratory tract infection, aged 1 month to 8 years (includes reference ¹²⁷)	14 positive EIA for <i>Chlamydia</i> genus antibodies; 12 positive species-specific MIF (7 <i>C. trachomatis</i> , 3 <i>Cpn</i> , 2 <i>C. psittaci</i>)	9/12 MIF-positive chlamydial infections (4 <i>C. tr.</i> , 2 <i>Cpn</i> , 2 <i>C. ps.</i>) had bronchial obstruction.
Hahn 1995 ¹³	46 adults with stable moderate persistent asthma	All had MIF titers $\geq 1:16$, 2 were culture positive on more than one occasion prior to treatment	25/46 had major (18) or complete (7) symptom improvement confirmed by pulmonary function testing after 4–6 weeks of macrolide or doxycycline treatment.
Gnarpe et al 1996 ¹³¹	210 children with acute respiratory infections, aged 0–15 years	Positive throat PCR (40)	8 PCR positive children had asthma.
Biscione et al 1998 ¹³²	78 infants and children admitted to hospital with wheezing and bronchiolitis	Positive PCR in respiratory secretions	37% PCR-positive: 18% in patients aged less than 3 months to 58% in those aged over 5 years.
Kamesaki et al ¹³³	33 Japanese children with an asthma exacerbation	Acute antibody titer rise (12) and/or positive culture (8)	15 (45%) were diagnosed with <i>Cpn</i> infection (7 acute antibody, 3 culture positive, 5 both)
Hahn et al 1998 ¹⁴	Outpatient primary care and allergy practices	<i>Cpn</i> IgG titers of 1:512 (3)	3 patients (13, 45 and 65 years old) with severe, steroid-dependent asthma were able to discontinue oral steroids after 6–16 weeks of macrolide treatment.
Hahn et al ¹⁵	10 adult outpatients with a first-ever wheezing episode	MIF seroconversion in all 10 (8 primary, 2 secondary infections)	5/10 followed prospectively developed chronic asthma; another patient was culture-positive during development of chronic bronchitis.

* Microimmunofluorescence test.

† Enzyme immunoassay.

‡ Chronic obstructive pulmonary disease.

§ Polymerase chain reaction.

that inclusion of criterion (3) in epidemiologic studies of acute respiratory illnesses such as pneumonia (particularly in older individuals) could result in an inflated estimate of *Cpn* as a cause.¹¹¹ To address this problem, it is recommended that future studies report results of criteria (1) and (2) separately from criterion (3). In the clinical evaluation of individual patients with severe respiratory disease, on the other hand, the 1:512 criterion can be life-saving.⁹⁵

Chronic Infection

As discussed above, criteria for serodiagnosis of chronic infection are not established. Persistent detection of serum IgA and/or chlamydial immune complexes have been associated with acute and chronic coronary artery disease syndromes^{112,113} but within-individual correlation of antibody and organism detection in vascular tissue can be inconsistent.¹¹⁴ Asthma has been associated with serum and/or secretory IgA antibody^{65,115} but not with immune complexes.⁶⁵ Although *Cpn* MIF serum IgA antibody testing is specific, it is probably not highly sensitive in the detection of chronic lung infection because serum IgA may not always be detectable in the presence of mucosal infection⁹⁴ and also because of variations in sensitivity of reagents used to detect IgA (S-P Wang: personal communication).

Seroepidemiologic techniques appear promising in studies of chronic lung infection in large populations but organism detection methods (such as PCR and ICC of bronchial lavage and bronchial biopsy specimens) are required to make a definitive diagnosis in individual patients.

Treatment

A large number of in vitro studies document adequate minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) against *Cpn* for tetracyclines, macrolides (including the azalide azithromycin), and newer quinolones. The relevance of these in vitro techniques for predicting eradication of *Cpn* in vivo

are unclear.¹¹⁶ Beta-lactam antibiotics can suppress infectivity but are not chlamydicidal. As previously mentioned, beta-lactams can produce abnormal RB morphology that resembles the persistent state.²² Sulfonamides demonstrate no activity against *Cpn*. Clinical experience has shown that traditional courses (7 to 10 days) of treatment with the "cidal" antibiotics listed above often result in clinical relapse; therefore longer courses (2 to 3 weeks) have been recommended for the treatment of acute *Cpn* respiratory infections.¹¹⁷ In persistent respiratory infections, the small amount of available data suggest that 3 weeks or more of treatment may be required for clinical remission.¹³ Persisting clinical improvement in asthma has been observed in culture-positive children after administration of prolonged courses of clarithromycin (500 milligrams twice daily)¹² and in adolescent and adult asthma patients after 4 to 6 weeks of azithromycin (1 gram orally, once per week) or doxycycline (100 milligrams orally, twice daily) administration.^{13,14} As previously mentioned, post-treatment persistence of *Cpn* following clinical improvement has been observed.^{43,44} It is not known whether eradication of *Cpn* from upper respiratory tract secretions indicates that the organism has also been eradicated from deeper tissues.

Two unresolved problems in designing appropriate treatment regimens for persistently infected patients are (1) the duration of extracellular survival of *Cpn* EBs is unknown and (2) persistently infected cells contain RBs that may be relatively resistant to antibiotics. Elementary bodies are metabolically inactive and are not killed by antibiotics. If EB survival time is longer than the duration of treatment, *Cpn* might not be eradicated. The in vitro model of chlamydial persistence is characterized by RBs that are metabolically downregulated and therefore possibly relatively resistant to antibiotics. It is therefore important to distinguish acute from chronic respiratory infection when designing appropriate antibiotic regimens. For example, the

duration of treatment ranges from 3 to 12 months in trials of chronic *Cpn* infection in atherosclerosis and myocardial infarction.¹¹⁸

CHLAMYDIA PNEUMONIAE IN ASTHMA AND COPD: CURRENT EVIDENCE

Tables 1 to 4 summarize the current published evidence linking *Cpn* infection with asthma and COPD.

Asthma

Case Reports (Table 1)

Nine case reports provide indications that *Cpn* infection can (1) precipitate wheezing during acute lower respiratory tract infections in nonasthmatic individuals, (2) exacerbate established asthma, and (3) initiate asthma in previously asymptomatic individuals. Furthermore, three case reports suggest that asthma associated with infection can be improved after antibiotic treatment. Eosinophilia was reported on in two infected asthma patients and resolved after treatment in one case.

Case Series (Table 2)

Fourteen uncontrolled case series include more than 100 subjects with asthma and either (1) documented *Cpn* infection (organism detection and/or serodiagnostic criteria met) or (2) lacking serodiagnostic criteria but having serologic findings and response to antibiotic treatment suggestive of chronic infection. These case series contain additional suggestive data supporting a role for *Cpn* infection in acute wheezing and in the exacerbation, initiation and promotion of asthma in both children and adults. Three case series reported improvement in asthma after antibiotic treatment in culture-positive asthma patients and/or in asthma patients meeting serodiagnostic criteria.¹²⁻¹⁴ Additional patients with possible chronic infection (nondiagnostic levels of "pre-existing" or "chronic" antibody) also responded to treatment.¹³

Since *Cpn* infection is prevalent in the general population, it can be

Table 3. *Chlamydia pneumoniae* (Cpn) Infection and Asthma: Controlled Studies

Reference	Study population	Cases	Controls	Findings of Cpn infection
Hahn et al 1991 ⁷¹	Adult outpatients with acute lower respiratory illness	A. Wheezing (61) B. Cpn titer >1:64 (71)-exposed	A. Nonwheezing (304) B. Cpn titer <1:16 (71)-unexposed	<u>Polyvalent (IgM, IgA, IgG) titer ≥1:64:</u> A. Cases 33%, controls 17%, OR 2.1 (1.1-4.2)* <u>Asthmatic bronchitis within 6 months after illness:</u> B. Cases 30%, controls 7%, OR 7.2 (2.2-23.4)*
Hahn et al 1994 ¹²⁸	Adults with acute wheezing or nonwheezing respiratory illnesses	A. Chronic asthma (12) B. Acute wheezing (30)	A. & B. Nonwheezers (89)	<u>Polyvalent (IgM, IgA, IgG) titer ≥1:16:</u> A. Cases 100% v controls 53% (P < .001) B. Cases 80% v controls 53% (P < .001)
Peters et al 1994 ¹⁴⁹	Adult patients with acute respiratory illness (ARI) and well controls	Asthma exacerbation (46)	A. Nonasthma ARI (53) B. Matched controls without ARI (23)	<u>IgM ≥ 1:16, IgG ≥ 1:512 or 4-fold titer rise, cases 22% versus:</u> A. controls 8% (P < .001) B. controls 4% (P < .001)
Emre et al 1994 ¹²	Inner city children aged 5 to 16 with acute asthma and well controls	A. Asthma patients (118)	A. Healthy age- and sex-matched controls (41)	<u>Culture positive:</u> A. Cases 11%, controls 5% (P = NS)
Weiss et al 1995 ¹³⁹	Adults with bronchospasm and asymptomatic controls, aged 18-79	A. Adults with bronchospasm (68)	A. Asymptomatic controls (26)	<u>IgG ≥ 1:16:</u> A. Cases 87%, controls 92% (P = NS)
Emre et al 1995 ¹⁵⁰	45 children with and without culture-proven Cpn infection	Culture-positive asthma (14)	A. Culture-positive pneumonia (11) B. Culture-negative asthma (11) C. Culture-negative asymptomatic (9)	<u>Cpn-specific IgE by immunoblot, cases 86% versus:</u> A. controls 9% (P < .001) B. controls 18% (P < .001) C. controls 22% (P < .006)
Emre et al 1996 ¹⁵¹	56 patients with cystic fibrosis, aged 1-47	A. Hospitalized for an acute pulmonary exacerbation with pulmonary function deterioration (32)	A. Clinically stable (24)	4 cases v. 0 controls were Cpn culture-positive; 3 of 4 culture-positive cases were wheezing. <u>Positive Cpn-specific IgE by immunoblot:</u> 4/4 culture-positive cases, 2/18 culture-negative cases, 6/20 controls (P = .003)
Hahn et al 1996 ⁶⁵	Adult primary care outpatients with recent-onset (<2 y) asthma and matched controls, aged 27-80	A. Asthma patients (25)	A. Asymptomatic controls with normal pulmonary function (45)	<u>IgA titer ≥1:10:</u> A. Cases 72%, controls 44%, OR 3.7 (1.1-9.0)* <u>IgG titer ≥1:16:</u> A. Cases 92%, controls 84% (P = NS)

* Adjusted odds ratio (95% confidence interval).

† Bronchial provocation test with methacholine.

‡ Secretory IgA from nasal aspirate.

§ *Chlamydia pneumoniae* Asthma Roxithromycin Multinational (CARM) study.

Table 3. Continued

Reference	Study population	Cases	Controls	Findings of <i>Cpn</i> infection
Hahn et al 1996 ¹⁵²	104 adult outpatients with asthma	A. Infectious asthma (beginning after an acute respiratory illness) (68)	A. Noninfectious asthma (atopic, occupational or exercise-induced) (36)	IgA titer $\geq 1:16$: A. Cases 62%, controls 22% ($P = .0002$) IgG titer $\geq 1:16$: A. Cases 93%, controls 61% ($P < .01$)
Peeling et al 1996 ⁶³	Same as above	Same as above	Same as above	IgG antibodies against chlamydial heat shock protein-60: A. Cases 19%, controls 3% ($P = .03$) 5 chsp-60 positive patients had IgE antibodies (immunoblot) against <i>Cpn</i> 60, 62 and/or 70 kDa antigens
Björnsson et al 1996 ¹³⁴	Subjects with asthma-related symptoms (122) and general population controls (75) aged 20–44	A. Wheezing B. Bronchial hyperresponsiveness (BHR) [†]	A. No wheezing B. No BHR	IgM $\geq 1:16$ and/or IgG $\geq 1:512$: A. OR 6.7 (1.3–35.7)* IgA $\geq 1:32$: B. Cases 22%, controls 8%, OR 3.3 (1.3–8.3)
Brüggen et al 1996 ¹⁵³	Adult intrinsic asthma patients and general population controls	A. Stable asthma without exacerbation (100)	A. General population controls (number not stated)	Throat antigen detection by <i>Cpn</i> monoclonal antibody immunofluorescence (IF) test: A. Cases 70%, controls 27% ($P < .001$)
Cook et al 1998 ¹⁴⁰	Asthma patients and nonasthmatic hospitalized controls, aged 15–88	A. Acute asthma (123) B. Severe stable chronic "brittle" asthma (46)	A. & B. Nonasthmatic hospitalized controls (1518)	IgM ≥ 8 and/or IgG ≥ 64 and/or IgA ≥ 8 : A. Cases 20%, controls 18% ($P = NS$) IgG $\geq 1:64$ and ≤ 256 : B. Cases 35%, controls 13%, OR 3.99 (3.6–9.9)*
von Hertzen et al 1998 ¹³⁵	Consecutive patients with asthma or allergy, aged 15 years and older	A. All asthma (332) B. Atopic asthma (183) C. Nonatopic asthma (149)	A. Symptomatic, nonasthmatic controls (98) B. Atopic controls (30) C. Nonatopic controls (68)	IgG $\geq 1:128$: A. Cases 34%, controls 17%, OR 2.6 (1.4–4.8)* B. OR 2.1 (0.7–5.8)* C. OR 3.3 (1.4–7.7)*

argued that *Cpn* infection in asthma, including an apparent treatment benefit, is entirely coincidental. The uncontrolled treatment results documented in Table 2 require confirmation by performance of randomized, controlled trials before firm conclusions can be reached regarding the efficacy of antibiotics in asthma. The reported preva-

lence of asymptomatic *Cpn* carriage, as determined by culture or PCR, was 0% of 51 healthy college students in Seattle,¹⁰¹ 2% of 104 asymptomatic health care workers from Brooklyn, NY,¹²⁵ 5% of 234 healthy persons from Sweden,¹²⁶ and 6% of 93 apparently healthy Swedish children.⁷⁷ Whether *Cpn* infection is more prevalent in

asthma than in control groups is addressed in the next section.

Controlled Studies (Table 3)

Eighteen controlled studies from 8 countries that include over 4000 cases/controls show that positive markers of *Cpn* infection are significantly associ-

Table 3. Continued

Reference	Study population	Cases	Controls	Findings of <i>Cpn</i> infection
Miyashita et al 1998 ¹⁵⁴	Adults with acute asthma exacerbations and nonasthmatic controls	A. Acute exacerbations of asthma (168)	A. Matched controls attending the same hospital (108)	<p>IgG \geq1:16: A. Cases 85%, controls 68% ($P < .001$)</p> <p>IgG geometric mean titer (GMT): A. Cases 39, controls 18 ($P < .0001$)</p> <p>IgA \geq1:16: A. Cases 48%, controls 17% ($P < .001$)</p> <p>IgA GMT: A. Cases 17, controls 6 ($P = .0001$)</p> <p>IgM \geq1:16 or IgG \geq1:512 or 4-fold titer rise: A. Cases 9%, controls 3% ($P < .05$)</p>
Larsen et al 1998 ⁶⁴	Danish adults with bronchial asthma and healthy controls	A. Adults with asthma (22)	A. Healthy controls (25)	<p>IgG \geq1:16: A. Cases 22%, controls 24% ($P = \text{NS}$)</p> <p>Presence of <i>Cpn</i>-specific IgE: A. Cases 69%, controls 68% ($P = \text{NS}$)</p>
Cunningham et al 1998 ¹¹⁵	108 children with asthma, aged 9–11 years, followed prospectively for 13 months	<i>Cpn</i> PCR and sIgA \ddagger obtained in 292 exacerbation episodes	65 children provided specimens when asymptomatic	<p>PCR positive: (1) Cumulative rate 45% (23% of symptomatic v 28% asymptomatic episodes) (2) PCR+ associated with multiple exacerbations ($P < .02$)</p> <p>sIgA\ddagger antibodies: Higher levels associated with multiple exacerbations ($P < .02$)</p>
Blasi et al 1998 ¹⁵⁵	Adult Italian CARM§ study screenees and healthy blood donors	120 adult asthmatics	163 blood donors	<p>PCR positive: 5/120 cases v 0/163 controls ($P = .059$)</p> <p>IgG \geq1:64: Cases 34%, controls 22% ($P = .03$)</p>

ated with asthma in 15 of 18 studies. Positive markers for infection included PCR detection, immunofluorescent staining of throat specimens, serodiagnostic antibody titers, other titers of total Ig and/or isotypic (IgA and IgG) antibodies, anti-heat shock protein 60 (hsp60) antibodies, *Cpn*-specific serum IgE antibodies, and secretory IgA antibodies in respiratory secretions. The rigor with which asthma was defined was variable. The initial report of

associations with wheezing, asthmatic bronchitis, and adult-onset asthma did not uniformly employ objective measurements of pulmonary function in the case definition.⁷¹ This deficiency was remedied in a followup study that reported significant positive associations of *Cpn* antibodies and pulmonary function confirmed asthma.¹²⁸ All subsequent reports stated or implied the use of objective criteria in the definition of asthma. A single population-

based study employed bronchial hyper-reactivity measured after methacholine inhalation.¹³⁴

Serologic markers for *Cpn* infection have been associated with nonatopic,^{71,135} adult-onset¹³⁶ asthma. Nevertheless, *Cpn* PCR positivity is quite prevalent in childhood asthma,^{115,132} suggesting that delayed antibody development could account for some of the age-related serologic patterns. Serologic markers for *Cpn* infection are

Table 4. *Chlamydia pneumoniae* (*Cpn*) Infection and Chronic Obstructive Pulmonary Disease (COPD): Controlled Studies

Reference	Study population	Cases	Controls	Findings of <i>Cpn</i> infection
Beatty et al 1991 ¹⁴⁶	Veterans Administration Medical Center patients	A. Inpatients with acute exacerbations of COPD (41) B. Outpatients with stable COPD (65)	A. & B. Age- and sex-matched Urology Clinic outpatients without airflow obstruction (24)	IgG $\geq 1:16$: A. Cases 82% v controls 75% ($P = NS$) B. Cases 77% v controls 75% ($P = NS$)
Blasi et al 1993 ¹⁶²	Italian outpatients recruited from an academic medical center	A. Patients with an acute purulent exacerbation of COPD (142)	A. Asymptomatic internal medicine clinic outpatients (114)	IgG $\geq 1:64$: A. Cases 63% v controls 46% ($P < .01$) IgG $\geq 1:512$: A. Cases 14% v controls 5% ($P = .03$) IgM $\geq 1:16$: A. Cases 4% v controls 0% ($P = .07$)
von Hertzen et al 1995 ¹⁶³	Finnish military and civilian adult patients with lower respiratory tract disease	A. COPD patients (46)	A. Patients with acute community-acquired pneumonia (CAP) (51)	IgM $\geq 1:20$ or 4-fold titer rise: A. Cases 2% v controls 14% ($P = .06$) Persistent IgG $\geq 1:128$ and IgA $\geq 1:40$: A. Cases 54% v controls 4% ($P < .0001$) Positive sputum IgA by MIF: A. Cases 52% v controls 8% ($P < .0001$) Positive sputum sIgA* EIA: A. Cases 51% v controls 10% ($P < .0001$) Positive sputum IgG by MIF: A. Cases 24% v controls 14% ($P = NS$)
von Hertzen et al 1996 ¹⁶⁴	Finnish elderly male COPD subjects and population controls	A. COPD inpatients with acute exacerbations (36) B. Population-based subjects with COPD (54)	A. & B. Population-based controls without respiratory illness (321)	IgA $\geq 1:16$: A. Cases 89% v controls 55% ($P < .001$) B. Cases 66% v controls 55% ($P = NS$) IgG $\geq 1:32$: A. Cases 86% v controls 91% ($P = NS$) B. Cases 87% v controls 91% ($P = NS$) IgA GMT†: A. Cases 70 v B cases 108 v controls 95 ($P = NS$)

* Secretory IgA.

† Geometric mean titer.

‡ Polymerase chain reaction test.

also associated with “infectious asthma,” ie, a history that asthma began after an acute respiratory illness such as bronchitis or pneumonia.^{137,138} These associations with specific clinical manifestations support the concept

that asthma is a multifactorial syndrome.¹³⁶

Of the three completely negative studies in Table 3, one reported solely on culture positivity¹² and another reported only on IgG antibody in a pop-

ulation characterized by an unusually high prevalence of seroreactivity (92%) in the control group.¹³⁹ The third negative study⁶⁴ compared asthma cases, most of whom were atopic, with nonatopic controls. The study by Cook et al¹⁴⁰

Table 4. Continued

Reference	Study population	Cases	Controls	Findings of <i>Cpn</i> infection
von Hertzen et al 1997 ¹⁶⁵	Finnish elderly hospitalized or ambulatory COPD patients, hospitalized CAP patients	A. Severe COPD (FEV1 <50% pred) (41) B. Moderate COPD (FEV1 ≥50% pred) (13)	A. & B. CAP patients (23)	<u>PCR± positive:</u> A. Cases 59% v B. cases 40% v controls 21% (<i>P</i> = .047) <u>Positive sputum sIgA:</u> A. Cases 80% v B. cases 58% v controls 14% (<i>P</i> < .0001) <u>Positive immune complexes:</u> A. Cases 51% v B. cases 39% v controls 15% (<i>P</i> = .025) <u>IgA GMT±:</u> A. Cases 59 v B cases 22 v controls 7 (<i>P</i> < .0001) <u>IgG GMT±:</u> A. Cases 120 v B cases 79 v controls 47 (<i>P</i> = .01)
Miyashita et al 1998 ¹⁶⁶	Japanese adults with an exacerbation of COPD and matched controls encountered at a medical school hospital clinic	A. COPD (77)	A. Controls (120)	<u>IgG ≥1:16:</u> A. Cases 96% v controls 73% (<i>P</i> < .0001) <u>IgG GMT±:</u> A. Cases 73 v controls 20 (<i>P</i> = .0001) <u>IgA ≥1:16:</u> A. Cases 70% v controls 18% (<i>P</i> < .0001) <u>IgA GMT±:</u> A. Cases 24 v controls 7 (<i>P</i> = .0001)

found significant serologic associations for severe asthma but not for mild asthma. The latter analysis has also been criticized for lack of comparability between cases and controls.¹⁴¹

Methodologic deficiencies were not limited to negative studies. Potential confounders of *Cpn* marker prevalence in both case and control groups include geographic location,¹⁴² presence of a *Cpn* epidemic,¹⁴³ age,¹⁴⁴ sex,¹⁴⁴ smoking,¹⁴⁵ sampling frame (hospital versus community-based sampling)¹⁴⁶ and occupational status (clinic¹⁴⁷ and hospital workers¹²⁵ and possibly other groups such as firefighters and police officers¹⁴⁷ have greater than expected rates of *Cpn* seroreactivity). For cases, atopic status and age of asthma onset influence the prevalence of positive serologic markers.^{71,136} Several studies also suggest that asthma severity is a significant covariate, with markers of

Cpn infection being more common in severe disease.^{132,140,148} Potential cross-reactions between *Cpn* and *C. trachomatis* antibodies have been noted in one study¹³⁴ but not in others.^{65,71} Many of these potential confounding variables were not fully accounted for in the studies listed in Table 3. Larger prospectively designed and better controlled population-based epidemiologic studies will soon augment the information provided by this first generation of studies.¹³⁶

The preponderance of positive associations between markers of *Cpn* infection and asthma can suggest but cannot prove causation. *Chlamydia pneumoniae* antibody associations with asthma might not indicate more previous exposure or chronic infection at all but instead might reflect the known association of asthma with a Th2 bias (towards increased antibody produc-

tion and decreased cell-mediated immunity). That a Th2 bias is not responsible for the serologic associations found in Table 3 is suggested by a report that *Cpn* antibodies are associated with adult-onset asthma but not with childhood onset-asthma, even when antibody in the latter group is measured in adulthood.¹³⁶ The specificity of the association (present for *Cpn* but absent for *C. trachomatis*⁷¹) also argues against the importance of Th2 bias as an explanation. The antibody associations reported in Table 3 might also indicate noncausal previous exposure or chronic *Cpn* infection. On the other hand, several groups of investigators have hypothesized that *Cpn* infection produces chronic inflammation and bronchial hyperreactivity in susceptible individuals.^{12,71,115} Conclusive evidence must be sought in studies to detect *C. pneumoniae* in the lungs of

asthma patients, in further studies of disease pathogenesis and in randomized, controlled treatment trials.

COPD (Table 4)

Smoking is a known risk factor for COPD. Smoking is also quantitatively associated with increased levels of *Cpn* serum antibodies both in subjects with COPD¹⁵⁶ and in populations without COPD.^{113,145,157,158} In one study, smoking was also associated with increased levels of chlamydial immune complexes.¹⁵⁹ Possible explanations for these findings are that smoking facilitates *Cpn* lung infection, promotes deeper penetration of *Cpn* into lung tissue, or both, to produce a greater antibody response.

Acute *Cpn* infection can be diagnosed in up to 5% of acute exacerbations of chronic bronchitis and COPD and the frequent detection of *Cpn* serologic markers in COPD is a nonrandom finding that suggests chronic infection in many cases.¹⁶⁰ Table 4 presents data on six controlled epidemiologic studies of *Cpn* infection markers in COPD. Five of six studies found positive associations with a variety of markers including PCR, MIF antibodies, secretory IgA and immune complexes. The single negative study reported only on IgG antibodies that were also very prevalent (75%) in the control group.¹⁴⁶ It has been hypothesized that chronic *Cpn* infection may (1) facilitate access of different pathogens to the lower airways¹⁶¹ and (2) amplify smoking-associated inflammation in the bronchi of patients with COPD and contribute to the development of irreversible airway obstruction.³ No treatment studies of chronic *Cpn* infection in COPD have been published.

SUMMARY

Available evidence strongly supports a role for acute *Cpn* respiratory tract infection as a trigger for wheezing and asthma exacerbations, although acute respiratory viral infections remain the most common culprits. It also appears that acute infection can initiate asthma in some previously asymptomatic patients but the

quantitative role for *Cpn* as an asthma initiator is unknown at the present time. Whether chronic *Cpn* infection plays an important role in contributing to persistent asthma symptoms and/or to asthma severity is unclear and additional information will have to be available before definite conclusions regarding these possibilities can be reached.

Extrapolation of currently available *Cpn*-asthma data to clinical settings must be done cautiously. Two recommendations can be suggested at this time: (1) Clinicians who manage severe persistent asthma that is not well controlled using conventional anti-inflammatory therapies should evaluate these patients for *Cpn* infection or even consider empiric antibiotic treatment in selected cases.¹⁴ (2) It is appropriate to obtain *Cpn* testing during the earliest stages of asthma onset, particularly (but not exclusively) when asthma begins during or after an acute respiratory illness,¹⁵ since there is evidence that treatment of documented infections in the early stages of asthma can result in long-lasting remissions.¹³ Existing data are insufficient to support generalized recommendations pertaining to other patients with asthma.

Concern has been expressed that untreated persistent infection could contribute to the accelerated decline in lung function noted in a poorly characterized subgroup of asthma patients. *Chlamydia pneumoniae* infection has been associated with rapid development of fixed obstruction in a patient who developed new, severe asthma.¹⁴ There is as yet, however, no evidence that inflammation caused by chronic *Cpn* infection causes airway remodeling. This possibility deserves further investigation but should not influence clinical practice at this time, except to note that evaluation for *Cpn* infection is reasonable in an asthma patient who demonstrates a rapid loss of lung function.¹⁴

It is important to remember that, in the primary care setting if not in the allergist's office, most acute wheezing during respiratory illnesses does not result in chronic asthma and does not require antibiotic treatment.¹⁶⁷ The di-

agnosis of asthma should be supported by objective measurements of reversible airway obstruction as well as by clinical criteria. Diagnostic testing for *Cpn*, if available, should be done prior to consideration of antichlamydial antibiotic treatment in selected asthma patients. It would be unfortunate indeed if the growing but still inconclusive evidence supporting a role for infection in asthma is overinterpreted and results in increasing misuse of antibiotics.

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CME Examination

No 009-010

Questions 1-20. Hahn DL. *Ann Allergy Asthma Immunol* 1999;83:271-292.

CME Test Questions

1. *Chlamydia* species were once considered as viruses because they:
 - a. are not susceptible to antibiotics
 - b. do not stain with Gram's reagent
 - c. do not grow on conventional media
 - d. are obligate intracellular organisms
 - e. none of the above
2. The chlamydial life cycle includes all of the following stages except:
 - a. an extracellular metabolically active infectious particle termed an elementary body (EB) that is susceptible to antibiotics
 - b. EB attachment and cell entry via endocytosis into target host cells
 - c. inhibition of endolysosomal fusion and differentiation into reticulate bodies (RBs)
 - d. differentiation of EBs from RBs
 - e. release of EBs into the extracellular environment to complete the life cycle
3. Which one of the following immunopathogenic substances accumulates within atypical chlamydial reticulate bodies in in vitro models of chlamydial persistence?
 - a. major outer membrane protein (MOMP)
 - b. chlamydial heat shock protein-60 (chsp-60)
 - c. interferon-gamma (IFN- γ)
 - d. tumor necrosis factor alpha (TNF- α)
 - e. none of the above
4. Blindness in trachoma and tubal infertility in pelvic inflammatory disease are strongly associated with host immune response to:
 - a. major outer membrane protein (MOMP)
 - b. chlamydial heat shock protein-60 (chsp-60)
 - c. interferon-gamma (IFN- γ)
 - d. tumor necrosis factor alpha (TNF- α)
 - e. none of the above
5. Persistent detection of organism-specific serum IgA antibodies suggests chronic infection because:
 - a. chronic infections always produce IgA antibodies
 - b. IgA antibodies are easier to measure than IgG antibodies
 - c. IgA antibodies are only produced in chronic infections
 - d. IgA antibodies are produced in response to mucosal infections
 - e. the half-life of serum IgA is short (about 1 week), therefore persistent detection implies persistent antigenic stimulation
6. *Chlamydia pneumoniae* persistent infection in humans is suggested by which of the following observations?
 - a. PCR positivity within circulating monocytes of general population subjects
 - b. culture positivity after treatment of acute *C. pneumoniae* respiratory infections
 - c. repeated culture isolation in patients with respiratory illnesses including asthma
 - d. none of the above
 - e. all of the above
7. Currently, no experimental evidence has been reported for which one of the following potential immunopathologic effects of *C. pneumoniae*?
 - a. *Chlamydia pneumoniae*-specific IgE in infected asthma patients
 - b. immune responses to chsp-60 in asthma patients
 - c. chlamydial LPS activity in the lungs of patients with bronchial hyperreactivity
 - d. ciliary dysfunction in *C. pneumoniae*-infected human lung tissue
 - e. In vitro production of cytokines by *C. pneumoniae* infection of mononuclear cells
8. The average proportion of community-acquired pneumonia attributed to *C. pneumoniae* worldwide is closest to which of the following estimates?
 - a. 1%
 - b. 10%
 - c. 25%
 - d. 32%
 - e. The average prevalence is unknown
9. The average incidence of wheezing (acute and chronic) after *C. pneumoniae* infection worldwide is closest to which of the following estimates?
 - a. 1%
 - b. 10%
 - c. 25%
 - d. 32%
 - e. The average incidence is unknown
10. Which one of the following viruses has been associated with

- chronic infection in patients with obstructive airways disease?
- RSV
 - parainfluenza
 - adenovirus
 - rhinovirus
 - herpes virus
- Which of the following is the most sensitive and specific serologic test for diagnosis of acute *C. pneumoniae* infection in adults?
 - the microimmunofluorescence (MIF) test
 - the complement fixation (CF) test
 - detection of chlamydial immune complexes
 - detection of IgM antibodies against chsp-60
 - detection of IgM antibodies against chlamydial LPS
 - Which one of the following serologic responses is present in acute primary *C. pneumoniae* respiratory infection and absent in secondary (re)infection?
 - A serum IgA response
 - A serum IgM response
 - a four-fold or greater rise in IgG antibody titer in serum specimens obtained 6 weeks apart
 - an IgG titer of 1:512 or greater if paired sera are not available
 - presence of secretory IgA
 - A minimum estimate of the worldwide adult population infected by *C. pneumoniae* is:
 - 1%
 - 10%
 - 25%
 - 32%
 - 50%
 - C. pneumoniae* infection has not been associated with which one of the following asthma syndromes?
 - "brittle" (severe) asthma
 - adult-onset asthma
 - acute bronchitis with wheezing (acute asthmatic bronchitis)
 - asthma in children
 - exercise-induced asthma
 - Which of the following has not been reported concerning *C. pneumoniae*-COPD associations?
 - PCR positivity
 - sputum IgA positivity
 - serologic responses suggesting chronic infection
 - prevention of further development of fixed obstruction by treatment
 - smoking-associated promotion of *C. pneumoniae* infection
 - Which one of the following antibiotic classes has no bacteriostatic or bacteriocidal activity against *C. pneumoniae*?
 - beta-lactams
 - sulfonamides
 - quinolones
 - tetracyclines
 - macrolides
 - Which one of the following antibiotic classes is bacteriostatic but not bacteriocidal against *C. pneumoniae*?
 - beta-lactams
 - sulfonamides
 - quinolones
 - tetracyclines
 - macrolides
 - The recommended duration of antibiotic treatment for acute *C. pneumoniae* respiratory infection is:
 - 5 days
 - 7 days
 - 14 to 21 days
 - 3 months
 - none of the above
 - Uncontrolled clinical observations suggest that successful outcome after treatment of *C. pneumoniae* infection in symptomatic asthma patients is most dependent on:
 - identifying the organism in the nasopharynx
 - using a macrolide instead of a tetracycline antibiotic
 - choosing an appropriately long duration of treatment
 - treating only patients with an IgG titer greater than 1:256
 - treating only mild disease
 - A search for *C. pneumoniae* infection might be helpful in which of the following clinical situations?
 - steroid-dependent asthma
 - asthma not responding to anti-inflammatory treatment
 - asthma beginning after a bout of pneumonia or bronchitis
 - asthma with a rapid development of fixed obstruction
 - all of the above

Answers to CME examination—Annals of Allergy, Asthma, & Immunology (Identification No 009-009)
 Letko E, et al: Tacrolimus (FK 506). *Ann Allergy Asthma Immunol* 1999;83:179-190

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|------|-------|-------|-------|
| 1. e | 6. c | 11. a | 16. c |
| 2. e | 7. e | 12. b | 17. b |
| 3. d | 8. e | 13. c | 18. d |
| 4. c | 9. b | 14. a | 19. a |
| 5. e | 10. e | 15. b | 20. b |