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Editor-in-Chief  
**Charles W. Stratton, MD**  
Vanderbilt University  
School of Medicine  
Nashville, Tennessee

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## Association of *Chlamydia pneumoniae* with Chronic Human Diseases

Charles W. Stratton, MD  
Vanderbilt University School of Medicine  
Nashville, TN 37232

### Introduction

*Chlamydia pneumoniae* was initially recognized as a cause of acute lower respiratory tract infections such as pneumonia and bronchitis in both adults and children (1-7), hence the species name "*pneumoniae*." Moreover, *C. pneumoniae* was noted in some individuals to cause a persistent respiratory tract infection following an acute infection (8), which is entirely consistent with the known chronic nature of chlamydial infections (9,10). In addition, *C. pneumoniae* has been shown to establish a subclinical asymptomatic respiratory tract infection (11).

### Pathogenesis of Chronic Chlamydial Infections

Establishment of persistent low-grade infections in the lung by *C. pneumoniae* creates an important factor for the pathogenesis of this microorganism. The ability of *C. pneumoniae* to infect a wide variety of human cells, including epithelial, endothelial, and smooth muscle cells as well as macrophages and monocytes, is well documented (12-20). The infection of macrophages, in particular, allows *C. pneumoniae* to enter the circulation from pulmonary tissues and cause systemic dissemination. The tendency for *C. pneumoniae* to disseminate from the initial site of infection in the lung has been described in the murine model of infection (21,22). Similar dissemination is presumed to occur in humans. Indeed, the presence

of *C. pneumoniae* DNA in peripheral blood mononuclear cells (PBMCs) has been well documented (23-29). Moreover, the viability of *C. pneumoniae* in circulating PBMCs has recently been established (30). The ability of *C. pneumoniae* to cause persistent infections combined with its ability to disseminate via the vascular system has raised questions as to the role of this pathogen in a number of chronic human diseases (31-33). Viable *C. pneumoniae* circulating in PBMCs may reach various human tissues after an inflammatory trigger event occurs in the tissue and then cause chronic infection in the tissue. This might create or worsen a chronic disease process. The purpose of this article is to review the association of *C. pneumoniae* with chronic human diseases.

### Chronic Lung Diseases

The predilection of *C. pneumoniae* to cause acute respiratory tract infections combined with its persistent nature suggests that it might play a role in chronic lung diseases (34). Chronic obstructive pulmonary disease (COPD) is a slowly developing irreversible and generally progressive chronic lung disease in which three disorders are commonly included: chronic bronchitis, peripheral airway disease, and emphysema. Indeed, *C. pneumoniae* has been found to be a frequent cause of acute exacerbations of COPD (35). Accordingly, it has been suggested that *C. pneumoniae* may have a role in the pathogenesis of COPD (36). Immunohistochemical staining for *C. pneumoniae* is increased in lung tissue from

subjects with COPD, suggesting that persistent infection with this organism is common (37). In addition, morphological findings by electron microscopy in pulmonary emphysema reveal aberrant chlamydiae that are identical to those seen in atherosclerosis (38). Persistent low-grade infection of the lung by *C. pneumoniae* is thus likely to contribute to chronic lung disease and, in some instances, may even be causal.

### Chronic Otolaryngeal Diseases

Otolaryngeal infections include sinusitis, otitis media, pharyngitis, tonsillitis, and laryngitis. These infections may be acute, recurrent, or chronic. The seroprevalence of antibodies to *C. pneumoniae* suggests that this microorganism is an important and common pathogen of otolaryngeal disease (39). *C. pneumoniae* has been isolated from both acute and chronic otitis media (40,41), and polymerase chain reaction (PCR) studies have confirmed and extended these early observations (42,43). Isolation of *C. pneumoniae* from the maxillary sinus has been described in one case report (44), but additional studies evaluating the role of *C. pneumoniae* in sinusitis have not been done. *C. pneumoniae* has been isolated from pharyngeal tissue biopsies as well as demonstrated by

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immunohistochemical methods in patients with chronic pharyngitis (45). Similarly, immunohistochemical analysis and PCR have demonstrated *C. pneumoniae* in adenoid tissue from children undergoing adenoidectomy for hyperplastic adenoids (46,47). Clearly *C. pneumoniae* is present in otolaryngeal tissues and plays a role in both acute and chronic infections as well as a possible role in a hyperplastic response.

### Asthma

Infection has long been thought to play a role in asthma (48). For example, respiratory tract infections are thought to precipitate wheezing in many asthmatic patients. The recent use of PCR to diagnose viral infections of the respiratory tract has documented the role of rhinovirus and respiratory syncytial virus in acute exacerbations of asthma (49). As *C. pneumoniae* is a pathogen causing acute and chronic respiratory tract infections, it may play a similar role in asthma. One of the first studies to investigate this possibility found that there is an association of *C. pneumoniae* infection with wheezing, asthmatic bronchitis, and adult-onset asthma (50). Not only did *C. pneumoniae* appear to exacerbate asthma, it seemed in some patients to initiate asthma. The authors concluded that repeated or prolonged exposure to *C. pneumoniae* may have a causal association with wheezing, asthmatic bronchitis, and asthma. Other investigators have confirmed the association of *C. pneumoniae* with acute exacerbations of asthma in both adults and children (51-58). Several studies suggest that antimicrobial therapy against *C. pneumoniae* is beneficial in the course of reactive airway disease (59-61). Whether or not *C. pneumoniae* plays a causal role in addition to its role in exacerbations of asthma remains to be determined.

### Atherosclerosis

Despite significant advances in our understanding of the various risk factors involved in atherosclerosis, there are significant gaps in the elucidation of the etiology of vascular injury and atherogenesis. Chronic infection of vascular tissue has received considerable attention recently as an inducer of vascular injury and subsequent development of atherosclerosis. Although infection with a variety of infectious agents such as cytomegalovirus has been implicated in atherogenesis, the best evidence to date links the presence of *C. pneumoniae* with the pathogenesis of atherosclerosis. Saikku et al. (62,63) first reported an association between anti-*C. pneumoniae* antibody titers and coronary artery disease. In a 1999 review, Wong, Gallagher, and Ward (64) reported that 21 of 27 studies showed "some sort of positive serological association between positive anti-*C. pneumoniae* titers and atherosclerosis." Similar results have been reported in cerebrovascular accidents with a number of studies showing a positive correlation with anti-*C. pneumoniae* antibodies (65-67). Direct evidence of *C. pneumoniae* infection of blood vessels is provided by studies using electron microscopy (68,69,74), PCR (69,71-78,82), immunohistochemistry (68,70-75,80,82), reverse transcriptase PCR (79), and cultures (75,77,80,81). Finally, animal models support a role for *C. pneumoniae* in the pathogenesis of atherosclerosis (83-85).

### Neurological Diseases

The serologic association of *C. pneumoniae* infections with neurological diseases began with several individual case reports that linked this microorganism with Guillain-Barre syndrome (86) and lumbosacral meningoradiculi-

tis (87). These observations were followed by additional reports associating *C. pneumoniae* with meningitis (88,89). The association of chlamydial infections with neurological syndromes has been strengthened by a large serological survey of patients with neurological disease (90). These observations suggest that *C. pneumoniae* may be more prevalent as an associated agent in central nervous system (CNS) diseases than appreciated (90) and that chlamydial infections should be included in the differential diagnosis of neurological syndromes (91). The first direct evidence that *C. pneumoniae* infection may be risk factor for a chronic neurological disease was a study that demonstrated that *C. pneumoniae* is present, viable, and transcriptionally active in areas of neuropathy in the Alzheimer's disease brain (92). This was followed by a report of a case in which *C. pneumoniae* was isolated from the cerebrospinal fluid (CSF) of a patient with multiple sclerosis (MS) (93). Anti-chlamydial therapy markedly improved the course of MS in this patient. A more extensive study by the same investigators demonstrated that infection of the CNS is a frequent occurrence in MS patients (94). Other investigators have confirmed the presence of *C. pneumoniae* in CSF from MS patients (95,96) as well as in CSF from patients with other types of neurological disease (97). Additional case reports for meningoencephalitis and encephalomyelitis (98,99) suggest that *C. pneumoniae* is a neurotrophic pathogen and thus may play a role in a variety of chronic neurological diseases.

### Chronic Rheumatological Diseases

Rheumatological diseases include those diseases that involve the connective tissues. Joints and related structures of

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the skeleton are considered the principal connective tissues and vary widely in structure and function as well as in predisposition to disease. Many connective tissue diseases in humans are chronic and involve inflammation. The most common is rheumatoid arthritis (RA). RA is a chronic connective tissue disease of unknown etiology which has been considered by some to be the result of a chronic inflammatory synovial response to an unrecognized antigen, such as that from infectious agent(s). Vasculitis is a recognized component of many chronic rheumatological diseases (100) including RA (101). Vasculitis has been associated with a number of infectious agents (102). The recognition that *C. pneumoniae* may induce isolated and systemic vasculitis in small and large blood vessels (103) has therefore raised questions as to its role in chronic rheumatological diseases. Moreover, *Chlamydia* species are known to cause polyarthritis in calves and sheep (104-107). Thus, it is not surprising to find that *C. trachomatis* is now recognized as a cause of reactive arthritis (108-112). Similarly, *C. pneumoniae* also has been associated with reactive arthritis (113-118). It is possible that *C. pneumoniae* could also play a role in RA. Such a role may be secondary infection of inflamed joints, or it may be causal. The observations that antimicrobial therapy with tetracyclines, agents active against *Chlamydia* species, is beneficial for some patients with rheumatoid arthritis (119-122) suggests that chlamydial infection may be a factor.

In addition, *C. pneumoniae* has been associated with other chronic rheumatological diseases. One case report has found an association of *C. pneumoniae* with systemic lupus erythematosus in which the patient was cured by a combination of clarithromycin, prednisolone, and cyclophosphamide (123). More intriguing is the association of *C. pneumoniae* with temporal arteritis. Temporal arteritis is a clinical manifestation of giant-cell arteritis. Giant-cell arteritis is a vasculitis of unknown etiology that predominantly affects medium- and large-sized arteries (124). Giant-cell arteritis and a closely related clinical syndrome, polymyalgia rheumatica, affect the elderly and often involve an acute onset with flu-like upper respira-

tory tract symptoms. For this reason, an infectious process has been proposed as a trigger mechanism (125). An initial case in which *C. pneumoniae* DNA was detected in an artery specimen has been reported (126). A more extensive investigation found that *C. pneumoniae* was present in temporal artery specimens from most patients with giant cell arteritis (127). This study detected *C. pneumoniae* by both immunohistochemistry and PCR and noted that the dendritic cells in the adventitial layer of the arteries may represent the antigen-presenting cells. This work further supports the association of *C. pneumoniae* with chronic rheumatological diseases.

### Cancer

Chronic infections are known to predispose to malignant growth. As *C. pneumoniae* may cause chronic infections, it may predispose to cancer. There is serological evidence of an association between *C. pneumoniae* infection and lung cancer. In one study, chronic *C. pneumoniae* infection was positively associated with the incidence of lung cancer and was especially increased in men younger than 60 years (128). This has been corroborated by a second study showing that chronic *C. pneumoniae* infection is common in patients with lung cancer (129). Another serological study found evidence of an association between chronic *C. pneumoniae* infections and malignant lymphoma (130). In cutaneous T-cell lymphoma, there is a protein that has been identified and found to be stimulatory for malignant Sezary T cells. This protein has been termed Sezary T-cell activating factor and is often present in the skin of patients with mycosis fungoides, the predominant form of cutaneous T-cell lymphoma. This Sezary T-cell activating factor has been found to be a *C. pneumoniae*-associated protein (131). Therefore, it is possible that *C. pneumoniae* may play a role in the pathogenesis of cutaneous T-cell lymphoma.

### Miscellaneous Chronic Diseases

*C. pneumoniae* has been associated with a number of other chronic diseases. It is not surprising that *C. pneumoniae* has been reported as a treatable cause of chronic fatigue syndrome (132). It is likely that many chronic infections would result in patients experiencing

chronic fatigue; thus, a chronic chlamydial infection would be expected to do the same. Fibromyalgia and other myalgia of unknown cause have been described in patients with chronic fatigue syndrome; *C. pneumoniae* antibodies have been linked with myalgia of unknown cause, including fibromyalgia (133). An interesting association of *C. pneumoniae* infections with diabetic nephropathy has been noted (134). This is interesting because of the possible relationship between glucose metabolism and chlamydial infection. For years, it has been speculated that chlamydiae are energy parasites that are totally dependent on their host cells for ATP and other high-energy intermediates (135), although this concept has been questioned recently due to the complete sequencing of genes from *C. trachomatis* and *C. pneumoniae*. Analysis of these chlamydial genes suggests that chlamydiae have some functional capacity to produce their own ATP and reducing power (136). Nonetheless, it is clear that infection of eukaryotic cells with chlamydiae results in an increase in the rate of glycolysis and that this increase is not caused by chlamydial metabolic activity but instead is a host cell response to the infection (137,138). This might offer an advantage for chlamydial replication in a host with diabetes and increased levels of glucose. If this were the case, chlamydial infection might be the source of the accelerated atherosclerosis known to occur in diabetics. An association of *C. pneumoniae* infection with pyoderma gangrenosum/skin ulcers in diabetic patients has been described (139,140). *C. pneumoniae* therefore might be an important pathogen in diabetic patients. Finally, an association of *C. pneumoniae* and interstitial cystitis has recently been described (141). Interstitial cystitis (IC) is a chronic inflammatory disease occurring primarily in females. IC is considered a sterile bladder condition characterized by symptoms of urgency, frequency, and pain. The etiology of IC is unknown, but autoimmune mechanisms have been thought to play a role. Analysis of urine samples of IC patients by PCR revealed that 71% of patients with IC were positive for *C. pneumoniae* (141). Therefore, bladder biopsies were done for culture of this pathogen. Of those patients with IC, 82% (14/17)

had tissue cultures positive for *C. pneumoniae* (141). Control patients were limited to those patients without a history of irritative voiding symptoms, transitional cell carcinoma, or recurrent urinary tract infection. In these control patients, 16% (1/6) had tissue cultures positive for *C. pneumoniae*. This difference was statistically significant ( $P = 0.004$ ). Thus, *C. pneumoniae* may have a role in the pathogenesis of IC.

## Summary

It is apparent from this review that *C. pneumoniae* has been implicated in many chronic diseases of humans. Whether the role is that of innocent bystander, cause, or perhaps something in between remains to be determined. Regardless of the role of *C. pneumoniae* in these or other chronic diseases, this microorganism is becoming a major health concern. Considerable resources will be needed to determine its role in human disease. If *C. pneumoniae* proves to play an important role in any or all of these chronic diseases, its eventual control or eradication may do much to improve the health of countless persons.

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The editors and the publisher of *Antimicrobics and Infectious Diseases Newsletter* invite you to contribute either a lead article or a case report. Of special interest are papers which discuss the appropriate use of antimicrobial agents. Case Reports should be concise papers and contain a) a brief clinical history of the illness; b) description of cultures or tests performed; c) antibiotics or antimicrobial agents administered; d) result of treatment. In addition, letters expressing opinions or offering insights on technical ideas and procedures will be considered for publication (subject to editing) providing they are signed by the authors and do not exceed two typewritten pages.

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Statens Serum Institut  
Division of Microbiology  
5 Artillerivej  
2300 Copenhagen S  
Denmark  
Tel: +45-3268 3535  
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e-mail: rsk@ssi.dk

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Address editorial correspondence to Charles W. Stratton, MD, Director of Clinical Microbiology, Department of Pathology, Vanderbilt University Medical Center, Room 4524-TVC, The Vanderbilt Clinic, Nashville, TN 37232. e-mail: charles.stratton@mcmail.vanderbilt.edu

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