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Chlamydia Infection and Pneumonia

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1. INTRODUCTION

A wide spectrum of human diseases can result from chlamydial infections. Psittacosis is an infectious disease of avians caused by *Chlamydia psittaci* that can manifest in severe systemic disease in humans.[1] *Chlamydia trachomatis* infections are the leading cause of sexually transmitted genital tract disease, the only cause of classic trachoma, and also result in perinatal infant pneumonia and conjunctivitis acquired from the infected mother during childbirth.[2] *Chlamydia pneumoniae* causes a variety of acute respiratory illnesses, including pharyngitis, sinusitis, bronchitis, and pneumonia, and has been associated with chronic cardiopulmonary diseases including adult-onset asthma[3] and atherosclerosis.[4] Although *C. psittaci, C. trachomatis,* and *C. pneumoniae* each have been associated with a distinct array of human diseases, pneumonia is common to all three. Pneumonias caused by each species have both unique and shared features and consideration of these differences and similarities may provide insight into mechanisms of these chlamydial diseases. For this reason, the current chapter examines the epidemiology, pathogenesis, clinical symptoms, and immune response to chlamydial pneumonias.

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2. CHLAMYDIAL BIOLOGY

Chlamydiae are intracellular bacteria with unique morphology and a biphasic life cycle.[5] Two functionally and morphologically distinct forms can be identified during the growth cycle: the infectious elementary body (EB) and the replicative reticulate body (RB). The EB is a small (0.1 to 0.2 μm), metabolically inert form that can survive extracellularly, contains no peptidoglycan, and instead may maintain structural integrity via a network of disulfide crosslinkages involving two cysteine-rich proteins and/or the major outer membrane protein (MOMP). In contrast, the RB is larger (0.8 to 1 μm) and noninfectious, but synthesizes DNA, RNA, and proteins to divide by binary fission. As chlamydiae cannot synthesize adenosine triphosphate (ATP) or nucleotides *de novo*, RBs must acquire host cell energy and nutrients to replicate and the bacterium must parasitize a eukaryotic host cell to survive and multiply.

The life cycle begins when the EB binds a host membrane receptor and becomes endocytosed by unknown mechanisms. Once internalized, the organisms are detectable in membrane-bound phagosomes and incorporate host-cell sphingolipids into the inclusion membrane[6 8] without interfering with Golgi-mediated exocytosis of glycoproteins.[9] Chlamydiae block phagolysosomal fusion and begin to reorganize EBs into RBs. RBs multiply by binary fission within phagosomes and revert back to EBs before the EB-filled phagosome ruptures. Chlamydial EBs then exit the cell to begin another round of replication. *In vitro* incubation and replication periods vary with different chlamydial species, serovars, and host cell types.

All chlamydiae can infect and multiply within epithelial cells, and *Chlamydia*–epithelial cell interactions have been extensively characterized.[10] Other cell types are less permissive to growth of most chlamydial species. Polymorphonuclear leukocytes (PMNs) ingest and destroy most *C. psittaci* and *C. trachomatis* EBs,[10] and growth within mononuclear phagocytes (Mϕs) is restricted for *C. trachomatis*.[11] *C. pneumoniae* and some strains of *C. psittaci* can replicate within Mϕs, and *C. pneumoniae* is unique in that it also can replicate in endothelial cells and smooth muscle cells.[12,13] This broad tropism may contribute to the diversity of diseases associated with *C. pneumoniae*. Importantly, the Mϕ has been proposed to mediate persistence and spread of chlamydiae *in vivo*,[14] and the alveolar macrophage may be a primary target cell in chlamydial pneumonias caused by all three species. The alveolar macrophage also may act as a vehicle to transport the organism to extrapulmonary sites, such as the liver for *C. psittaci*[15] and coronary arteries for *C. pneumoniae*.[16]

3. PSITTACOSIS

Psittacosis is a systemic zoonosis that can cause an atypical pneumonia in humans.[1] Disease severity and duration are variable, but mortality may be as high as 30% in untreated cases.

3.1. Epidemiology

C. psittaci normally infects birds and some domestic animals but can be transmitted to humans by aerosol droplets. Approximately 5% to 8% of birds are carriers for *C. psittaci* but 100% of birds may be infected in overcrowded or other stress-inducing environments.[1,17] Any bird is a potential hazard, as over 130 bird species have been shown to carry *C. psittaci;* infections acquired from turkeys or parrots are particularly virulent to humans. Severe illness is thought to result rarely from human-to-human transmission. The infection is most common in young and middle-aged adults, and most epidemiological studies do not find prevalence differences between genders. Although fewer than 200 cases of psittacosis are reported to the Centers for Disease Control each year, the severity of disease makes psittacosis a significant concern to poultry farmers, abattoir workers, and veterinarians.[1,17]

3.2. Pathogenesis and Symptoms

The onset of symptoms follows a 1- to 3-week incubation period. The organism initially establishes infection in the lung as most patients present with an atypical pneumonia characterized by fever, cough, and severe headache, and less frequently with sore throat and chest soreness.[1,18,19] Histology reveals inflamed trachea, bronchi, bronchioles, and alveoli, and mucous plugging is apparent; alveolar and interstitial exudates contain mostly infiltrating lymphocytes. Radiologically, psittacosis pneumonia is not distinguishable from other atypical pneumonias and X-ray films often show pneumonitis originating from the hilum during the first week and lower lobe consolidation afterwards, with pleural effusions seen in up to 50% of cases. These radiological abnormalities may take up to 5 months to resolve and underscore the severity of lung involvement in psitticosis.[1,18,19]

Although the lung is the organ most frequently involved in psittacosis, the disease can be systemic with damage to multiple organ systems. The mechanism of systemic spread is not known, but as *C. psittaci* can infect and survive within human, murine, and pig alveolar macrophages,[14,20–22] this cell type may contribute to spread of the organism. Neurological and gastrointestinal symptoms such as headache, malaise, vomiting, diarrhea or constipation, and nausea are common, but less common general symptoms such as sore throat, dyspnea, hemoptysis, rash, diaphoresis, and photophobia may complicate the diagnosis. If untreated, psitticosis may result in cardiac, hepatobiliary, neurological, and endocrine involvement with fatal consequences.[1,18,19]

3.3. Diagnosis and Treatment

The differential diagnosis of psittacosis includes other causes of atypical pneumonia including viral, *Mycoplasma, Coxiella, Legionella,* and *C. pneumoniae* pneu-

monia.[23] Common signs of psittacosis reported in greater than 50% of patients are fever, lung consolidation, and hepatomegaly. Splenomegaly may appear after the first week of onset of symptoms and together with arthralgia or myalgia may help focus the differential diagnosis.[1] An important epidemiological clue is exposure to birds.

The complement fixation assay (CFA), combined with clinical symptoms and a detailed history, currently is the most common diagnostic method for psittacosis,[24] but antigen detection methods such as enzyme immunoassay (EIA) and molecular methods such as the polymerase chain reaction (PCR) soon may provide more sensitive and specific methods of diagnosis. Treatment with tetracycline or doxycycline for up to 3 weeks reduces mortality to below 1%.

Very little is known about host immune responses to *C. psittaci* pneumonia. Immunity to *C. psittaci* infection has not been documented, and reinfections can occur.[24]

4. *C. TRACHOMATIS* PNEUMONIA

Unlike *C. psittaci, C. trachomatis* probably is not transmitted via respiratory droplets, although the organism can still cause pneumonia in both infants and adults. In infant pneumonia, *C. trachomatis* is transmitted during childbirth from the mother to the newborn, whereas in adult pneumonia *C. trachomatis* can establish lung infection in the immunocompromised individual, possibly by respiratory tract colonization or systemic dissemination from the genital tract. Cases of *C. trachomatis* pneumonia in immunocompetent adults have been reported in laboratory workers exposed to high titers of the organism,[25] but natural respiratory tract infection is very rare in individuals with intact immunity. *C. trachomatis* is a minor cause of pneumonia even in immunocompromised individuals,[26] but the resulting disease is severe,[26–30] in contrast to the mild pneumonia reported in immunocompetent infants. Thus, although the two syndromes are caused by the same organism, the diseases can manifest in different clinical symptoms, suggesting the contribution of distinct immune mediators in determining the severity of *C. trachomatis* pneumonia. Sections 4.1 to 4.3 discuss *C. trachomatis* infant pneumonia.

4.1. Epidemiology

Pneumonia in infants initially was associated with *C. trachomatis* when Beem and Saxon[31] detected the organism in 90% of infants with a distinct pneumonia syndrome characterized by a chronic, afebrile course, diffuse lung involvement and high serum immunoglobulins (Ig) G and M. Specific antibody titers to *C. trachomatis* also were elevated in these infants and no other respiratory pathogens were consistently associated with the pneumonia. Subsequent prospective studies[32–35] have indicated that 16% to 28% of infants born to *C. trachomatis*–infected mothers develop pneumonia and that the prevalence of disease is 1% to 5% in different communities.

4.2. Pathogenesis and Symptoms

The organism can infect numerous sites in the infant during childbirth including the conjunctiva, nasopharynx, rectum, and vagina.[36] Disease may manifest sequentially, as *C. trachomatis* can be recovered earlier in the conjunctiva compared to the nasopharynx[36] and half of infants with *C. trachomatis* pneumonia also have a history of conjunctivitis.[37] The onset of symptoms usually occurs within 8 weeks of birth when infants present with a staccato cough, tachypnea, and nasal discharge.[37] Importantly, the infants remain afebrile during the course of disease, and respiratory tract obstruction is uncommon.[37–39] Radiological findings may show diffuse interstitial infiltrates and bilateral hyperexpansion whereas pleural effusion and lobar consolidation are not present.[40] Hematological findings include peripheral eosinophilia and elevated serum IgG and IgM levels.[31,37] Although the disease is usually mild, very young infants may have severe symptoms[41,42] and untreated infants may remain ill for months.[31] Complications from acute *C. trachomatis* pneumonia are rare; however, follow-up studies on infants with *C. trachomatis* pneumonia report a significant increase of obstructive airway disease and asthma later in life, suggesting that infection may result in long-term respiratory sequelae.[43,44]

4.3. Diagnosis and Treatment

The recommended diagnostic method is culture of the organism from the pharynx followed by detection of chlamydial inclusions by immunofluorescent antibody staining.[45] The recommended treatment, oral erythromycin 50 mg/kg/day for 10 to 14 days, is only 80% effective and therefore a second antibiotic course may be required.[46,47] In many cases newer macrolides such as azithromycin or clarithromycin may be preferred, especially if the infant is intolerant to erythromycin.[48–51]

4.4. Host Immune Response to *C. trachomatis* Pneumonia

Pneumonia in infants is mild compared to the fulminant pneumonia observed in immunocompromised adults, suggesting that the immune response is important to protection from *C. trachomatis* pneumonia. However, the immune components involved in humans during *C. trachomatis* pneumonia are poorly understood. Instead, the immune mediators in this disease have been described extensively in animal models. These animal model studies are reviewed here, and pertinent correlations to the few human-based reports are provided.

Studies using an immunocompromised mouse model developed by Williams

et al.[52] have contributed valuable information about the immune response to *C. trachomatis* pneumonia. The authors initially observed that athymic nude mice (*nu/nu*), compared to their immunocompetent littermates (*nu/+*), were more susceptible to pneumonia caused by *C. trachomatis* (strain mouse pneumonitis, MoPn) as determined by increased mortality and decreased pulmonary clearance of the organism.[52] Transplantation of thymuses from *nu/+* mice to *nu/nu* resulted in increased resistance, indicating that T cells were important to protection.[52] The contribution of cell-mediated immunity (CMI) was demonstrated further when adoptive transfer of T cells from immunized *nu/+* mice to *nu/nu* mice conferred protective immunity in these animals.[53] Subsequent studies suggested a role for humoral immunity in protection as adoptive transfer of immune serum from *nu/+* to *nu/nu* mice increased resistance to intranasal MoPn challenge.[54] Indeed, human infants with *C. trachomatis* pneumonia had increased numbers of peripheral blood B cells that secreted large amounts of IgG, IgM, and IgA antibody in the absence of mitogens *in vitro*.[55] However, B-cell-deficient mice were as susceptible to MoPn as control animals, suggesting the importance of a multifactoral response to *C. trachomatis* pneumonia.[56]

The diversity of immune mediators involved in *C. trachomatis* pneumonia was supported further in histopathological studies with *nu/+*, *nu/nu*, and immunized *nu/nu* animals. These studies revealed that protection correlated with the presence of a variety of cell types including plasma cells, lymphocytes, monocytes, and macrophages.[57] A protective role for the latter also was indicated by the observation that alveolar macrophages were activated in infected *nu/+* (but not *nu/nu*) mice.[53] Importantly, Nakajo *et al.*[58] showed that human adult alveolar macrophages killed *C. trachomatis*, and the authors proposed that differences in bactericidal capacities of adult vs. infant alveolar macrophages[59,60] may explain the susceptibility of infants to *C. trachomatis* pneumonia; however, these studies did not examine the capacity of infant alveolar macrophages to kill *C. trachomatis*.

The presence of interferon-γ (IFN-γ)[61] tumor necrosis factor-α (TNF-α)[62] interleukin-1 (IL-1),[63] IL-6,[63] and transforming growth factor-β (TGF-β)[64] have been demonstrated in the lungs of immunocompetent mice inoculated with MoPn, and high serum levels of colony stimulating factors have been detected in infected *nu/nu* and *nu/+* mice.[65] Neutralizing antibody to IFN-γ[61] and to TNF-α[62] exacerbated disease in *nu/+* mice, indicating a protective role for these cytokines in *C. trachomatis* pneumonia. A protective role for IFN-γ also was suggested in a recent report by Yang *et al.*[66] using BALB/c mice, which die from *C. trachomatis* infection, and C57BL/6 mice, which are resistant to infection. These authors showed that BALB/c mice secreted higher levels of IL-10 and less IFN-γ compared with C57BL/6 mice that produced high levels of IFN-γ but minimal IL-10. Importantly, injection of neutralizing antibody to IL-10 initiated a delayed-type hypersensitivity (DTH) response in BALB/c mice,[66] indicating that IL-10 may inhibit Th1-like responses in BALB/c mice and that these Th1-like responses may be important in conferring immunity to C57BL/6 animals. Future studies with IFN-γ-knockout animals should elucidate further the role of this cytokine in *C. trachomatis* pneumonia.

Many of the protective components in the MoPn model for *C. trachomatis* pneumonia are similar to the MoPn model for *C. trachomatis* genital tract infections, recently reviewed by Cotter and Byrne.[67] Unlike in MoPn genital tract infections,[68] however, the role of specific T-cell subsets in MoPn pneumonia is not well understood. Recently, a dual role for γδ T cells, which may be induced following infection of *nu/nu* mice,[61] was suggested by Williams *et al.*[69] The authors showed that compared to control mice, γδ T-cell knockout mice and higher levels of pulmonary MoPn at days 3 and 7 but lower levels of MoPn at day 14,[69] suggesting that γδ T cells may be protective earlier but harmful later in *C. trachomatis* pneumonia. Additional studies are needed to elucidate the role of different T-cell subsets in MoPn pneumonia. Nevertheless, the MoPn murine model for *C. trachomatis* pneumonia has yielded valuable insight into immune responses during infection.

In summary, immunity to *C. trachomatis* pneumonia probably involves multiple cellular and cytokine-mediated effects, including induction of a T-cell-dependent CMI response with secretion of IFN-γ, activation of alveolar macrophages with subsequent secretion of TNF-α and other monokines, and recruitment of B lymphocytes followed by antibody production. Few studies have examined mediators of immunity to *C. trachomatis* pneumonia in humans and future work must focus on human cellular and molecular components involved in *C. trachomatis* pneumonias.

5. *C. PNEUMONIAE* PNEUMONIA

Of the three chlamydial species that cause diseases in humans, *C. pneumoniae* is the most common cause of chlamydial pneumonia in humans. *C. pneumoniae*, previously named the TWAR agent, was originally identified as an atypical strain of *C. psittaci*[70] in a mild epidemic of pneumonia in two northern Finnish communities. In 1989, *C. pneumoniae* received its own species designation,[71] partly due to its lack of DNA homology (<10%) with *C. trachomatis* and *C. psittaci*[72] and its unique, pear-shaped EB morphology.[73] Since its speciation 8 years ago, the organism has been recognized as an important cause of acute respiratory infections including community-acquired pneumonia, bronchitis, and sinusitis, and has been associated with a number of chronic pulmonary and extrapulmonary diseases including adult-onset asthma[3] and atherosclerosis.[4] Although clinical and epidemiological studies identify the organism as a major cause of community-acquired pneumonias (Table I), few studies thus far have examined the role of host immune responses to *C. pneumoniae* pneumonia.

TABLE I
Results of Major Clinical and Epidemiological Studies Examining the Role of *C. pneumoniae* in Community-Acquired Pneumonias

Year(s), location	Type of population	No. of cases	Percent of cases with etiologic diagnosis	Most common pathogen (% of cases)	Method(s) to detect *C. pneumoniae*†	No. *C. pneumoniae* diagnoses (% of cases)	Percent of *C. pneumoniae* cases with mixed etiology
1980–1 Seattle, USA[111]	Hospitalized patients	198	NR	Influenza A virus (11)††	Serology (MIF[a], CF)	20 (10)	NR
1981–4 Halifax, Canada[112]	Hospitalized patients	301	63	*Streptococcus pneumoniae* (9)	Serology (MIF[d])	18 (6)	61
1983–5 Seattle, USA[113]	University students	76	47	*Mycoplasma pneumoniae* (22)††	Serology (MIF[d], CF) and culture	9 (12)	NR
1983–7 Seattle, USA[98]	University students	149	32	*Mycoplasma pneumoniae* (11)††	Serology (MIF[a], CF) and culture	14 (9)	NR
1985 Little Rock, USA[114]	Hospitalized patients	154	51	*Legionella pneumophila* (8)	Serology (MIF[d])	12 (8)	33
1985–7 Gavle, Sweden[115]	Hospitalized patients	188	66	*Streptococcus pneumoniae* (20)	Serology (MIF[e])	23 (12)	52
1986–7 Oulu, Finland[116]	Hospitalized patients	125	88	*Streptococcus pneumoniae* (55)	Serology (MIF[b], CF)	54 (43)	66
1986–7 Pittsburgh, USA[117]	Hospitalized patients	359	66	*Steptococcus pneumoniae* (15)	Serology (MIF[d], CF)	22 (6)	NR
1987–8 South Africa[118]	Hospitalized patients	92	50	*C. pneumoniae* (21)††	Serology (MIF[g])	19 (21)	NR
1988 New Zealand[119]	Hospitalized patients	92	72	*S. pneumoniae* (33)	Serology (MIF, CF) and culture	1 (1)	NR
1990–1 Barcelona, Spain[82]	Outpatients, population-based study	105	44	*C. pneumoniae* (15)	Serology (MIF[f])	16 (15)	44
1991–2 Beer-Sheva, Israel[120]	Hospitalized patients	346	81	*S. pneumoniae* (43)	Serology (MIF[c])	62 (18)	69
1991–2 Berlin, Germany[121]	Hospitalized patients	236	68	*S. pneumoniae* (13)	Serology (CF, MIF[a]) and culture)	27 (11)	NR
1991–2 Milan, Italy[122]	Hospitalized patients	108	54	*M. pneumoniae* (14)	Serology (MIF[a])	14 (13)	0
1991–3 Scandinavia[123]	Hospitalized patients and outpatients	303	55	*S. pneumoniae* (14)	Serology (MIF)	26 (9)	20
1991–4 Halifax, Canada[84]	Outpatients	149	52	*M. pneumoniae* (23)††	Serology (MIF[a])	16 (11)	31
1991–4 San Patrignano, Italy[83]	Injection drug users in residential community, population-based study	210 total 149 HIV$^+$ 61 HIV$^-$	55 56 52	*S. pneumoniae* (18) *S. pneumoniae* (22) *C. pneumoniae* (26)	Serology (MIF[a])	36 (17) 20 (13) 16 (26)	11

(*continued*)

TABLE I
(Continued)

Year(s), location	Type of population	No. of cases	Percent of cases with etiologic diagnosis	Most common pathogen (% of cases)	Method(s) to detect *C. pneumoniae*†	No. *C. pneumoniae* diagnoses (% of cases)	Percent of *C. pneumoniae* cases with mixed etiology
1991–4 Murcia, Spain[124]	Hospitalized patients	342	29	*S. pneumoniae* (13)	Serology (MIF)	21 (6)	NR
1992–3 Multicenter study USA[85]	Ambulatory pediatric patients	260	47	*C. pneumoniae* (28)††	Serology (MIF[a]), culture	74 (28)	30
1992–4 Multicenter study Barcelona, Spain[100]	Hospitalized COPD patients	124	64	*S. pneumoniae* (26)	Serology (MIF[4])	9 (7)	22
1993–4 Multicenter study Ohio, USA[125]	Hospitalized patients	227	65	*C. pneumoniae* (18)	Serology (MIF[a]), PCR, culture	40 (18)	28
1995–6 Connecticut, USA[126]	Outpatients	50	54	*C. pneumoniae* (36)††	Serology (MIF[a]), PCR	18 (36)	NR

MIF = microimmunofluorescence; CF = complement fixation; PCR = polymerase chain reaction; NR = not recorded.
¶Adapted with permission from Kauppinen and Saikku.[103]
#Denotes mixed infections with pyogens.
†A four-fold rise in IgM or IgG titers by MIF was one diagnostic criterion used in all studies.
Additional MIF diagnostic criteria included: [a]IgM ≥ 16 or IgG ≥ 512[104]; [4]IgM ≥ 16, or IgG or IgA ≥ 512; [d]IgM ≥ 16 or IgA ≥ 64 or IgG ≥ 512; [e]IgM ≥ 32; [f]IgM ≥ 16; [g]presence of IgM; [h]IgG ≥ 512.
††Presence of *S. pneumoniae* not systematically sought.

5.1. Epidemiology

The population prevalence of *C. pneumoniae* in adults, as estimated by the microimmunofluorescence (MIF) test, is high (up to 50%) in all geographical locations examined.[74–77] Aldous *et al.*[78] used sera from a long-term family study to estimate an incidence of infection (70% asymptomatic) as 6% to 9% per year in children ages 5 to 14, and also noted declining incidence over time. Indeed, the prevalence of MIF antibody increases rapidly up to 40% to 50% between ages 5 and 20 but rises only gradually thereafter,[77] indicating that most primary infections occur in children and young adults. Even though a minority of *C. pneumoniae* infections probably result in pneumonia,[79] a role for the organism in severe community-acquired pneumonias requiring hospitalization has been reported in 2% to 43% of cases (Table I), with most estimates ranging between 6% and 18%. Because the pneumonia caused by *C. pneumoniae* also may be mild, many cases could go undetected[79–81] and the proportion of cases in the general population may be underestimated by hospital-based studies.

Since its first association with pneumonia less than 2 decades ago, *C. pneumoniae* has acquired a place among the top causes of community-acquired pneumonia in adults and also is important in children (Table I). Compared to pneumonia caused by *Streptococcus pneumoniae, C. pneumoniae* pneumonia frequently is milder and therefore may not lead as often to hospitalization or even to outpatient medical visits.[70] In adults, *S. pneumoniae* remains the number one cause of pneumonia in hospitalized patients, but two population-based studies in immunocompetent adults show *C. pneumoniae* as the most commonly identified pathogen in ambulatory patients diagnosed with pneumonia.[82,83] Studies targeting adult outpatients have detected *C. pneumoniae* in 11% to 36% of pneumonia cases.[82–84] Furthermore, a multicenter study in the United States[85] that examined in ambulatory pediatric population (ages 3 to 12) found a large number of cases attributable to *C. pneumoniae* (28%) and *M. pneumoniae* (27%), indicating a potential causative role for these atypical pathogens in the majority of pneumonias in this population.

5.2. Pathogenesis and Clinical Symptoms

C. pneumoniae initially is delivered by aerosol droplets into the upper respiratory tract, where it may cause ciliostasis[86] to gain access into the lungs. The organism has been shown to multiply within human alveolar macrophages[87] as well as endothelial cells[12] *in vitro,* which conceivably may serve as host cells during the infection. Growth of *C. pneumoniae* may initiate an inflammatory process, which induces lymphocyte recruitment[88] and subsequent manifestations of the pneumonia syndrome.

Although limited knowledge is available on the pathogenesis of *C. pneumoniae* pneumonia, intranasal infection of mice,[89–93] nonhuman primates,[94,95] and rab-

bits[96,97] has shown that (1) infected animals develop a prolonged, mild pneumonia with evidence of acute polymorphonuclear cell infiltrates and later, mononuclear cells; and (2) the organism can be isolated from extrapulmonary tissues. Upon reinfection, recovery of *C. pneumoniae* becomes increasingly difficult in both the murine[93] and cynomolgus monkey models,[95] suggesting that partial protective immunity occurs as a result of infection. These observations correlate well with human infections which often take a mild but chronic course, with reinfections resulting in fewer cases of pneumonia.[80,81,98]

Clinically, *C. pneumoniae* pneumonia resembles other atypical pneumonias, and symptoms specific for *C. pneumoniae* pneumonia do not exist. However, a number of characteristic features of *C. pneumoniae* pneumonia have been documented.[88] The incubation period is about 4 weeks,[99] and most cases develop with a gradual onset. Furthermore, often a biphasic illness is noted with initial onset of pharyngitis, hoarseness, and fever that may resolve before the onset of cough and other signs of lower respiratory tract illness.[88] Headache is another common symptom and auscultation often reveals rales, but neither finding is specific for *C. pneumoniae* pneumonia. Radiography may show pneumonitis in mild disease and pleural effusions in severe illness, but these findings also are not helpful in differentiating *C. pneumoniae* from other pneumonias.[38]

Although most *C. pneumoniae* pneumonias are mild, recovery from infection is slow even with antibiotic therapy[81] and severe cases do occur. An underlying disease such as chronic obstructive pulmonary disease (COPD) predisposes to *C. pneumoniae* pneumonia[100] and may aggravate the course of the disease. An important finding in *C. pneumoniae* pneumonias is the high rate of coinfection by *C. pneumoniae* and other organisms (Table I). This high coinfection rate observed in *C. pneumoniae* pneumonias suggests that the organism may predispose to pyogenic infections which may increase disease severity,[101] although additional studies are needed to address this hypothesis.

5.3. Diagnosis and Treatment

Diagnostic methods available to detect *C. pneumoniae* infection have been reviewed recently.[102,103] As Table I indicates, most studies make use of the MIF test to diagnose *C. pneumoniae* infections, and MIF has been useful in showing a high prevalence of *C. pneumoniae* pneumonias. However, because the prevalence of *C. trachomatis* infections also is high in selected populations, a certain portion of pneumonia patients may have cross-reactive antibodies to *C. trachomatis*. Comparison of results between studies (Table I) is further complicated because some groups define arbitrary MIF criteria for acute infection even though standard diagnostic criteria have been proposed.[104] Thus, as with other chlamydial species, *C. pneumoniae* diagnoses based solely on serological criteria are less preferable to diagnoses made by multiple methods.

In the absence of controlled trials, treatment with 2 g of tetracycline or erythromycin daily for a minimum of 14 days has been recommended. The newer macrolides clarithromycin and azithromycin also appear effective.[105] Notably, slow resolution and/or relapse after treatment are observed frequently.

5.4. Host Immune Response to *C. pneumoniae* Pneumonia

Little is known about the immune mechanisms involved in *C. pneumoniae* pneumonia. Yang *et al.*[89,93] infected mice with a high infective dose (10^7 infectious units) and observed an acute, patchy pneumonia with PMN infiltration and alveolar and bronchiolar exudate, followed by monocytic infiltration. Using a 10-fold lower inoculum, Laitinen *et al.*[106] observed a chronic inflammation developing gradually with perivascular and peribronchial lymphocytic infiltrations. Both groups reported histological changes for several weeks after infection and the organism could be isolated from the lungs of infected mice for up to 2 weeks following challenge. A strong antibody response that peaked 3 to 4 weeks after intranasal challenge also was present by EIA, and an inverse relationship existed between recovery of pulmonary infectious units and specific antibody titers. An IgM isotype was common in primary infections whereas IgG and IgA were markedly increased in reinfections.[81]

T-cell-lymphoproliferative responses to *C. pneumoniae* antigen were increased in patients with recent *C. pneumoniae* pneumonia,[107] suggesting a role for CMI in this disease. CMI responses may be modulated by *C. pneumoniae*–alveolar macrophage interactions, as *C. pneumoniae* induced the secretion of IL-1β, IL-6, and TNF-α by human monocytic cells[108] and IL-1β, IL-6, TNF-α, and IFN-α by human peripheral blood mononuclear cells.[109] The contribution of these cytokines to induction of cellular and humoral immune responses and the importance of these immune mediators in *C. pneumoniae* pneumonia currently are not understood. In murine models, corticosteroid administration during secondary infection allows recovery of previously noncultivatable organisms, suggesting that persistent infection may occur in the lung following the acute phase of pneumonia.[110] Thus in some cases the immune response to *C. pneumoniae* may suppress active infection but not totally eliminate the organism.

6. CONCLUSION

As outlined in Table II, this review has delineated similarities and differences in the epidemiology, pathogenesis, clinical symptoms, and immune responses to chlamydial pneumonias. Each organism may induce unique immune responses, as different pneumonia syndromes result from infection with different chlamydiae. Understanding such species differences in the context of one disease may help

TABLE II
Similarities and Differences between Chlamydial Pneumonias

	C. psittaci	*C. trachomatis*	*C. pneumoniae*
Epidemiology	Mainly zoonosis from birds, rare human-to-human transmission	Infant pneumonia from infected mothers during childbirth, adult pneumonia in immunocompromised individuals	Most common chlamydial pneumonia. Rare in infants and preschoolers; common in older children, adolescents, and adults
Pathogenesis	Primary infection in lungs, may become systemic. 1–3 week incubation period	Primary infection in infants results in mild pneumonia, may predispose to chronic pulmonary sequelae later in life. < 8 week incubation period	Primary infections and reinfections occur associated with chronic pulmonary and extrapulmonary diseases including adult-onset asthma, atherosclerosis. 3–5 week incubation period
Clinical symptoms	Initially as atypical pneumonia with fever, cough, headache, later with multiple organ-system involvement and fulminant psittacosis	Infant pneumonia—chronic, mild, afebrile disease with staccato cough. Adult pneumonia—acute, fulminant disease	Atypical pneumonia with gradual onset and biphasic illness (URT symptoms may resolve before LRT symptoms). Also severe pneumonia in hospitalized patients
Treatment	Tetracycline 500 mg q.i.d. or doxycycline 100 mg b.i.d. × 14–21 days	Erythromycin 50 mg/kg × 10–14 days	Tetracycline or erythromycin 2 g × 14 days. Newer macrolides (e.g., azithromycin, clarithromycin)
Immune response	Protective immunity not shown. Reinfections may occur.	Murine model exists. CMI, alveolar macrophages, humoral response (?) important. IFN-γ, TNF-α have protective effects. Little known on human immune responses.	Partial immunity as reinfections less severe in younger adults. CMI and alveolar macrophages may be important. Some animal models available.

CMI = cell-mediated immunity; URT = upper respiratory tract; LRT = lower respiratory tract.

establish common principles applicable to understanding the pathogenesis of these chlamydial infections. Clearly, the use of murine models for *C. trachomatis* pneumonia has described important immune mediators, and whether these mediators are equally applicable to recently developed *C. pneumoniae* animal models awaits to be seen. In either case, the immune response to pneumonia may be different in humans, and future studies therefore must define immune mediators in human chlamydial pneumonias.

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