

Role of *Chlamydia pneumoniae* in Acute Respiratory Tract Infections, Excluding Pneumonias

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Introduction

Chlamydia pneumoniae infection was first associated with community-acquired pneumonia (CAP) in 1985 and is now recognized as the third or fourth leading cause for CAP, accounting for about 10% of all cases of pneumonia worldwide. Acute infection with *C. pneumoniae* can also cause a broad range of upper and lower respiratory tract illnesses other than pneumonia. The purpose of this article is to review these non-pneumonic manifestations of acute *C. pneumoniae* infection, current laboratory techniques for diagnosis, and therapy.

Epidemiology

Seroprevalence studies indicate that infection with *C. pneumoniae* is common worldwide. In most populations, antibody prevalence is low in children below the age of five, rises rapidly throughout the school years and then persists throughout adulthood. In Seattle, Washington, for example, the seroconversion rate is 9% per year for children aged 5 to 9. Seroprevalence rates for children in some more densely populated countries, such as Japan, are even higher than in the United States and Western European countries. The seroprevalence patterns for *C. pneumoniae* and *Chlamydia trachomatis* are distinctly different. *C. trachomatis* antibodies are found in a minority of sexually active young adults but only rarely in older adults. Unlike *C. trachomatis*, *C. pneumoniae* seroprevalence persists and even continues to increase in older age groups, suggesting that reinfections or persistent infections are common for this organism throughout the human life span.

Prospective studies on stored sera show that the majority of seroconversions (up to 70%) are not associated with any significant complaints of respiratory illness. Thus, acute infections may

often be asymptomatic or are associated with trivial respiratory symptoms that do not trigger a medical encounter. The remainder of acute *C. pneumoniae* infections are associated with a wide variety of acute respiratory illnesses that will be reviewed in this article (Tables 2-6). Person-to-person spread appears to be slow and inefficient, at least under the living conditions experienced in Western industrialized societies. Mean time between illnesses has been reported as 28 days with the most frequent intervals being 17 to 23 days, suggesting that the true incubation period is about 3 weeks.

Diagnosis

Diagnostic techniques include organism identification and serologic testing (Table 1). Cell culture requires fastidious specimen handling, as the organism will be rendered nonviable if not cultured immediately, or slow frozen for later processing. Polymerase chain reaction (PCR) testing shows promise as the most sensitive detection method, but its use is currently limited to research laboratories. Direct immunofluorescence (DIF) testing is commercially available to detect *C. trachomatis* and preliminary evidence suggests that DIF may also be useful in rapid detection of *C. pneumoniae* in throat and sputum secretions. The most widely used serologic method is the microimmunofluorescence (MIF) technique originally developed by Wang and Grayston to study *C. trachomatis*. The MIF technique is species-specific, that is, it can distinguish seroreactivity due to the different species of chlamydia. However, the MIF test is time consuming, expensive, requires a trained microscopist, and is not widely available outside research settings. The genus-reactive chlamydia complement fixation (CF) test that is used to diagnose acute infection with *Chlamydia psittaci* (psittacosis) will be positive only in acute primary *C. pneumoniae* infections. Be-

cause many acute adult infections are secondary (reinfections), the CF test is relatively insensitive in older age groups.

Serodiagnostic criteria for acute infection are outlined in Table 1. All would agree that a fourfold antibody titer rise in specimens taken at least 4–6 weeks apart is indicative of acute infection. Most would agree that presence of species-specific IgM antibody also indicates acute infection, or at least recent

TABLE 1. Diagnostic Criteria for Acute *Chlamydia pneumoniae* Respiratory Tract Infection

Organism identification ^a	
Cell culture	
Polymerase chain reaction (PCR) test	
Immunofluorescent assays (DFA, IFA)	
Serologic criteria	
Species-specific microimmunofluorescence (MIF) test:	
4-fold or greater increase in IgM, IgA and/or IgG	
Single IgM titer $\geq 1:16$ or	
Single IgG titer $\geq 1:512$	
Primary (first exposure) infection:	
Presence of IgM, later appearance of IgG	
Secondary (re-exposure) infection:	
No IgM, rapid rise in IgG	

^aOrganism identification in the absence of serologic criteria may indicate chronic infection (all ages) or delay in acute antibody formation (children).

exposure, since IgM may persist for some months but then disappears. Several studies of young and middle aged adults with acute respiratory illnesses (bronchitis and pneumonia) also show excellent (but not perfect) agreement between organism identification and the presence of IgG antibody titers of 1:512 or greater. Good agreement between these serologic criteria for "acute antibody" and organism detection have been confirmed for children and teenagers with acute respiratory illnesses.

There are two caveats to consider when interpreting the serologic criteria presented in Table 1. First, some persistently culture-positive children with acute respiratory conditions have not developed antibody, even over many months of observation. Recently, other prospective observations have confirmed that seroconversion after infection (as defined by organism detection) may be delayed for over a year in some children. Also, a recent

study of Swedish children attending daycare centers found a PCR positive prevalence rate of 23%, well above previously reported seroprevalence rates for young children. Taken together, these data suggest that development of serum antibody after acute infection in young children may sometimes be delayed. Second, some asymptomatic, culture-negative (nasal- or oropharyngeal) adults from the general population have persisting IgG antibody titers of 1:512 or greater. This finding may be related to the high prevalence of *C. pneumoniae* DNA detected in peripheral blood mononuclear cells in patients with cardiovascular disease and in middle-aged blood donors. Thus, IgG titers of 1:512 or greater in asymptomatic adults may be due to persistent deep tissue infection and should not be interpreted as evidence of acute infection. However, in the setting of serious acute respiratory illnesses which could be caused by *C. pneumoniae*, most experts agree that treatment decisions based on the 1:512 criteria can be beneficial, sometimes even life-saving.

Non-pneumonic Respiratory Manifestations of Acute Chlamydia pneumoniae Infection

Table 2 illustrates the spectrum of non-pneumonic acute respiratory illnesses that can be caused by acute *C. pneumoniae* infection. Data in Table 2 is presented as the percentage of identified acute *C. pneumoniae* infections that resulted in a particular respiratory syndrome (bronchitis, otitis, pharyngitis, sinusitis, etc.). The denominator for each percentage is the total number of acute *C. pneumoniae* infections diagnosed in each of eight selected studies from North America, Europe, and Japan that also reported on the occurrence of a variety of illness manifestations (total of 477 cases of infection). For comparison, the proportions of pneumonia are also presented.

For most studies, pneumonia predominated and bronchitis was also common. Pharyngitis commonly accompanied manifestations of lower respiratory tract illness (LRTI), but was less common as a sole manifestation of acute infection. Laryngitis is also fairly common, but tonsillitis is rare. A clinical diagnosis of sinusitis also accompanied *C. pneumoniae* LRTI but was not as common as pharyngitis. Otitis media was less commonly reported but did occur. The relatively wide study-to-study variation in reported prevalence of these conditions probably reflects the heterogeneity of settings (population-based, primary care, referral practices), age groups, geographical sites, time periods, and (possibly) diagnostic methods used, among other factors.

Clinical Characteristics of C. pneumoniae Acute Respiratory Infections

In general, respiratory illnesses caused by acute *C. pneumoniae* infection are indistinguishable from illnesses caused by respiratory viruses and by *Mycoplasma pneumoniae*. *C. pneumoniae* can cause acute respiratory symptoms characterized as a "biphasic illness": first, acute pharyngitis that is sometimes severe (with or without laryngitis) followed by a brief period of improvement followed by LRTI. The sensitivity and specificity of the "biphasic illness" presentation for the presence of acute *C. pneumoniae* infection is unknown, however.

Many studies in the outpatient setting document that, compared to other etiologies, *C. pneumoniae* causes a more indolent respiratory illness that is slower to develop to the degree of severity likely to trigger a medical encounter. Thus, a long duration or persistent respiratory symptoms prior to seeing a physician increases the likelihood that *C.*

“clues” can benefit patients with respiratory illnesses.

Family Outbreaks

Excellent examples of the protean manifestations and presentations of *C. pneumoniae* infection may be found in descriptions of documented family outbreaks.

TABLE 2. Clinical Manifestations of Acute *Chlamydia pneumoniae* respiratory infection in Selected Patient Populations (% of *C. pneumoniae* infections with the clinical manifestation)^a

Author(s)	Population	Pneumonia	Bronchitis	Otitis media	Pharyngitis/ Laryngitis/ Tonsillitis	Sinusitis	Other
Grayston, 1988	30 Adult student outpatients from Seattle, Washington	40	47 ^c		7 (30) ^b	3 (17) ^b	
Kleemola, Saikku, et al. 1988	69 Young Finnish military conscripts during 4 pneumonia epidemics	99			1 (20) ^b		
Frydén, Kihlström, et al. 1989	90 Swedish patients with "ornithosis" later confirmed as <i>C. pneumoniae</i>	61	30 ^c			(18) ^b	
Hahn, Dodge, et al. 1991	19 Adult outpatients from Madison, Wisconsin	16 ^c	84 ^c		(37) ^b	(16) ^b	Influenza-like illness (26) ^b
Hashiguchi, Ogawa, et al. 1992	39 Patients at an ENT outpatient clinic in Tokyo, Japan		33	15	46	5	
Thom, Grayston, et al. 1994	21 Middle-aged and older outpatients from Seattle, Washington	10 ^c	57 ^c		10	14	URI (5), FUO (5)
Falck, Heyman, et al. 1994	33 Mainly adult Swedish outpatients	3	58		21	6	Rhinitis (9), Conjunctivitis (3)
Berdal, Scheel, et al. 1997	176 Norwegian patients identified during a respiratory epidemic	36	84 (cough)		32	3	

^aPrimary clinical diagnosis.

^bIn addition to the primary clinical diagnosis of bronchitis or pneumonia.

^cSome patients also had wheezing.

pneumoniae infection will be identified. In one study, a predictor of *C. pneumoniae* etiology (compared with respiratory viruses and *M. pneumoniae*) was the presence of abnormal breath sounds auscultated on physical examination. It is unknown whether acting on these clinical

Family #1

Yamazaki et al. reported on two culture-positive Japanese sisters, aged 5 and 3, who had pneumonia/otitis and acute bronchitis, respectively. The 5-year-old (index case) had 7 weeks of persistent cough without fever and otalgia unresponsive to beta-

lactam treatment before she was referred and *C. pneumoniae* was isolated. She improved but *C. pneumoniae* was isolated persist-

members, aged 10, 30, and 33 years of age, who developed prolonged respiratory illnesses that did not improve despite

TABLE 3. Proportion of Bronchitis Attributed to Acute *Chlamydia pneumoniae* Respiratory Infection in Selected Patient Populations (% of bronchitis caused by *C. pneumoniae* infection)

Author(s)	Population	Total cases of bronchitis (diagnostic tests used)	No. (%) due to <i>Chlamydia pneumoniae</i>	Comments
Grayston, Kuo, et al. 1986	University students from Seattle, Washington	63 (culture, acute antibody)	3 (5)	A biphasic presentation (severe sore throat and/or laryngitis later followed by cough) or wheezing were described
Katzman, Tipton, et al. 1991	University students from Berkeley, California	151 (culture, acute antibody)	2 (1)	Same as above. Conjunctivitis was also described in both cases
Hahn, Dodge, et al. 1991	Mainly adult outpatients from Madison, Wisconsin	338 (culture, acute antibody)	16 (5)	Sore throat, laryngitis and wheezing were common accompaniments. A biphasic presentation was sometimes noted
Ogawa, Hashiguchi, et al. 1992	Hospitalized children and adults, Japan	85 (acute antibody)	19 (22)	
Hashiguchi, Ogawa, et al. 1992	Patients at an ENT outpatient clinic in Japan	57 (acute antibody)	13 (23)	Only 1/38 asymptomatic controls had acute antibody
Thom, Grayston, et al. 1994	Middle-aged and older outpatients from Seattle, Washington	247 (PCR, acute antibody)	12 (5)	Wheezing noted in 25%. One patient developed persistent symptoms of new reactive airways disease
Ni, Wang, et al. 1995	Mainly adult patients from Beijing, China	81 (acute antibody)	6 (7)	Chronic bronchitis was statistically more frequent in patients with <i>C. pneumoniae</i> infection than those without ($p=.05$)
Wright, Edwards, et al. 1997	Adults presenting to the Vanderbilt University emergency department	65 (acute antibody)	13 (20)	All patients in this study had persistent cough lasting 2 weeks or more prior to enrollment; 20% also had evidence of pertussis
Jonsson, Sigurdsson, et al. 1997	General practice adult population in Iceland	140 (acute antibody)	1 (1)	

ently post-treatment, whereas her 3-year-old sister became culture-negative after treatment that improved her bronchitis.

Family #2

Ghosh et al. reported on three serologically diagnosed family

beta-lactam and sulfonamide therapy. The 30-year-old husband had sore throat, hoarseness and fever, and was off work for 3 weeks. Despite penicillin treatment, symptoms worsened with development of sinusitis and impaired hearing. After a 10-day course of tetracycline therapy (500 mg, four times daily) he made

a complete recovery. One week later, his 33-year-old wife had fever and upper respiratory tract symptoms that did not respond to trimethoprim/sulfa treatment. At the same time, their 10-year-old daughter had a "flu-like" illness; both mother and daughter made complete recoveries after tetracycline treatment. Three other children in this family gave a history of a "flu-like illness"

family members did not seroconvert and remained well. Clinical manifestations ranged from pneumonia and bronchitis (with and without pharyngitis) to a few days of dry cough that resolved without treatment. Only one patient showed a biphasic illness presentation. Again, respiratory illnesses were sometimes resistant to treatment with beta-lactams but macrolides were effective.

TABLE 4. Proportion of Otitis Media Attributed to *Chlamydia pneumoniae* Respiratory Infection in Selected Patient Populations (% of otitis caused by *C. pneumoniae* infection)

Author(s)	Population	Total cases of otitis media (diagnostic tests used)	No. (%) due to <i>Chlamydia pneumoniae</i>	Comments
Hashiguchi, Ogawa, et al. 1992	Children and adults seen at an ear, nose and throat outpatient clinic in Tokyo, Japan	34 (acute antibody)	6 (18)	Only 1 (3%) of 38 healthy controls had acute antibody. All serologically diagnosed patients improved with macrolide or tetracycline therapy
Ogawa, Hashiguchi, et al. 1992	Children and adults seen at an ear, nose and throat department in Tokyo, Japan, with otitis media with effusion (OME)	43 (culture of middle ear aspirates)	6 (14)	Cephalosporins and norfloxacin were ineffective; macrolides and doxycycline were effective in alleviating symptoms
Ah Goo, Hori, et al. 1995	Children aged 6 months to 12 years referred to a Washington State community hospital for myringotomy or tympanostomy tube placement (OME)	75 (PCR, culture and serology of middle ear aspirates)	0 (0)	All were considered to have chronic ear infections requiring ventilation; 44 patients (59%) had received multiple antibiotic regimens prior to testing
Storgaard, Østergaard, et al. 1997	Danish children with acute otitis media (AOM)	20 (PCR on middle-ear aspirates)	1 (5)	<i>Streptococcus pneumoniae</i> was also isolated in the PCR positive AOM case
	Danish children with otitis media with effusion (OME)	53 (PCR on middle-ear aspirates)	5 (9)	PCR positive in 8 samples from 5 children whose mean age was greater than that of the PCR-negative children with OME
Block, Hammerschlag, et al. 1997	Consecutive children with AOM or refractory AOM from rural Kentucky	101 (culture and PCR of tympanocentesis aspirate)	8 (8)	Copathogens were isolated in 6/8 cases; 2 additional patients with <i>C. pneumoniae</i> culture negative AOM and 2/50 healthy control children were positive by either culture or PCR in the nasopharynx

in the month preceding their parents' illnesses; all had serologic evidence of previous *C. pneumoniae* infection.

Family #3

Blasi et al. reported on eight members of two Italian families, six of whom seroconverted and/or had *C. pneumoniae* identified on pharyngeal swabbing. These six became ill while two other

family members did not seroconvert and remained well. Clinical manifestations ranged from pneumonia and bronchitis (with and without pharyngitis) to a few days of dry cough that resolved without treatment. Only one patient showed a biphasic illness presentation. Again, respiratory illnesses were sometimes resistant to treatment with beta-lactams but macrolides were effective.

Family #4

Falck et al. reported on three members of a Swedish family who had persistent respiratory symptoms for two and one-half

years. During this observation period, serology and PCR testing revealed a failure to eradicate *C. pneumoniae* despite several prolonged courses of macrolides or tetracyclines, although reinfection could not be ruled out as a cause for persistent detection.

studies is probably a result of different populations, diagnostic criteria, etc. By far the highest percentages due to *C. pneumoniae* for bronchitis, otitis, and tonsillitis/laryngitis were reported from an Ear, Nose, and Throat specialty clinic in Japan. Community-based rates were lower for all three conditions.

TABLE 5. Proportion of Pharyngitis/Tonsillitis Attributed to *Chlamydia pneumoniae* Respiratory Infection in Selected Patient Populations (% of pharyngitis/tonsillitis caused by *C. pneumoniae* infection)

Author(s)	Population	Total cases of pharyngitis/tonsillitis (diagnostic test used)	No. (%) due to <i>Chlamydia pneumoniae</i>	Comments
Komaroff, Aronson, et al. 1983	Adults outpatients with sore throat encountered in four general medical practices in New England	43 (four-fold titer increase)	9 (21)	The 43 tested patients were derived from a stratified random sample of 267 patients with pharyngitis only. An additional 496 patients with pharyngitis and other respiratory tract symptoms also had a 21% estimated prevalence of chlamydial infection.
Komaroff, Branch, et al. 1989				
Grayston, Kuo, et al. 1986	University students from Seattle, Washington	150 (culture, acute antibody)	1 (1)	No evidence for acute <i>C. pneumoniae</i> infection was found in 28 students with sinusitis and otitis media, or in 68 with fever of unknown origin (FUO).
Huovinen, Lahtonen, et al. 1989	Finnish adult outpatients with sore throat	106 (acute antibody)	9 (8)	An additional 9% had <i>Mycoplasma pneumoniae</i> and 23% had beta-hemolytic strep.
Hashiguchi, Ogawa, et al. 1992	Children and adults with tonsillitis seen at an ear, nose and throat outpatient clinic in Tokyo, Japan	52 - tonsillitis (acute antibody) 32 - laryngitis (acute antibody)	10 (19)	Only 1 (3%) of 38 healthy controls had acute antibody. All serologically diagnosed patients improved with macrolide or tetracycline therapy
8 (24)				
Hargreaves, Zajac, et al. 1994	US Airforce basic trainees with pharyngitis	226 (acute antibody)	4 (2)	1 (1%) of 118 asymptomatic basic trainees had acute antibody
Hone, Moore, et al. 1994	Children and adults admitted to an Irish hospital with severe, acute tonsillitis	51 (DFA, acute antibody)	0 (0)	DFA test was positive in one patient who did not seroconvert

C. pneumoniae as a Cause for Specific Non-pneumonic Respiratory Diagnoses

Tables 3 to 5 illustrate that *C. pneumoniae* has been documented as a cause for 85 (10%) of 1227 bronchitis cases (range 1 to 23%), 26 (8%) of 326 cases of otitis (range 0 to 18%), and 40 (8%) of 510 cases of pharyngitis/laryngitis/tonsillitis (range 0 to 24%). Again, the wide variation in prevalence noted between

Bronchitis

Some observations from the studies selected for Table 3 are that wheezing was often reported in conjunction with acute bronchitis. The clinical implications for this finding for the development of persistent wheezing and asthma are beyond the scope of this article. Interested readers are referred to a recent review. Of interest is the finding of Wright et al. that 20% of

patients with a persistent cough lasting more than 2 weeks were found to fulfill serologic criteria for acute infection. Conjunctivitis is rarely reported in *C. pneumoniae* infection.

Otitis Media

No conventional bacterial pathogen can be isolated in 20 to 40% of patients with acute otitis media (AOM), which is distin-

to cross-reactivities with *C. pneumoniae*. The percentage of pharyngitis in more recent community-based studies has been lower: 14 (3%) of 482 (range 1 to 8%). An interesting recent report illustrates the potential for chlamydial persistence: Falck et al. reported on a series of patients with chronic pharyngitis who had persistent detection by PCR in throat swabs and positive immunochemical staining evidence for presence of the organism

TABLE 6. Proportion of Miscellaneous Acute Conditions Associated with *Chlamydia pneumoniae* Infection in Selected Patient Populations (% of disease attributed to *C. pneumoniae* infection)

Author(s)	Population	Total cases (diagnostic test used)	No. (%) due to <i>Chlamydia pneumoniae</i>	Comments
Common cold				
Makela, Puhakka, et al. 1998	Young Finnish adults with common cold symptoms	200 (four-fold antibody titer rise)	4 (2)	Viral etiology was established for 138 (69%). Evidence of non-chlamydial bacterial infection was found in 3 patients (1 <i>M. pneumoniae</i> , 1 <i>H. influenzae</i> , 1 <i>S. pneumoniae</i>).
Sinusitis				
Hashiguchi, Ogawa, et al. 1992	Children and adults with sinusitis seen at an ear, nose and throat outpatient clinic in Tokyo, Japan	19 (acute antibody)	2 (11)	Only 1 (3%) of 38 healthy controls had acute antibody.
Bronchiolitis				
Khan and Polter 1996	Infants hospitalized with bronchiolitis in England	152 (PCR on nasal aspirate)	2 (1)	PCR for <i>Chlamydia trachomatis</i> was positive in 26 (17%) and was found in patients up to 2 years of age.
Kawasaki's Disease Numazaki and Chiba 1996	Japanese infants and children hospitalized with active Kawasaki Disease	72 (IgM antibody)	11 (15)	IgM antibody was found in 8 (3.5%) of 229 healthy age- and sex-matched controls ($P > 0.01$).

guished from otitis media with effusion (OME) that is chronic, asymptomatic, and less associated with bacterial pathogens. *C. pneumoniae* was identified by culture and/or PCR in a total of 20 (7%) of 292 middle-ear aspirates (7% of AOM and 6% of OME), suggesting that this organism should be added to the list of pathogens that is associated with both acute and chronic otitis media. Causation needs to be further assessed by response to treatment.

Pharyngitis/Tonsillitis

In 1983, Komaroff et al. first reported on 9 (21%) of 43 adults with pharyngitis who has fourfold titer increases in *Chlamydia trachomatis* antibodies that were later acknowledged to be due

in pharyngeal biopsies. They also reported that the optimal antibiotic regimen to eradicate these chronic *C. pneumoniae* infections was not found.

Sinusitis/Bronchiolitis

A few studies have reported on *C. pneumoniae* infection in the common cold, acute sinusitis, infant bronchiolitis and as a potential cause for Kawasaki disease (Table 6).

A syndrome termed "chlamydial cold" characterized by slight sputum (70%), chest pain (35%), nausea and vomiting (21%), fever for several days (40%), rhinorrhea (69%), malaise (60%), sore throat (51%), and very slight eye discharge (14%) was relatively common during an epidemic of *C. pneumoniae*

infection in a Japanese middle-school population. However, in a non-epidemic situation in a Finnish general population, *C. pneumoniae* infection was rarely (2%) identified as a cause for the "common cold." Studies from a referral-based ENT clinic population in Japan found that *C. pneumoniae* could be isolated from the maxillary sinus of a patient with purulent sinusitis and that *C. pneumoniae* was responsible for 2 (11%) of 19 cases of acute sinusitis (Table 6). The percentage of acute sinusitis due to this infection in the general population has not been reported. One case report of a patient who developed chronic sinusitis and bronchitis after an acute infection raises the possibility that persistent infection might lead to chronic respiratory sequelae. This possibility is intriguing but has not been sufficiently investigated.

Chlamydia pneumoniae as a cause for infant bronchiolitis appears to be rare but infection by *Chlamydia trachomatis* in this age group is worth considering as a possible treatable cause for persistent respiratory symptoms (Table 5). Finally, a serologic study of patients with Kawasaki's disease found that 15% of them had IgM antibody, suggesting acute *C. pneumoniae* infection. The clinical significance of this finding is currently unknown but also deserves investigation.

Recognition and Treatment

A few clinical clues may be helpful in enhancing the judicious use of appropriate anti-chlamydial antibiotics directed against the subgroup of patients with acute respiratory illnesses suspected to be caused by acute *C. pneumoniae* infection. It must be recognized, however, that the science supporting these recommendations is minimal and needs buttressing, and that readily available, accurate and inexpensive diagnostic testing would be highly desirable.

Clinical clues to acute *C. pneumoniae* infection that I have found correlate sometimes with diagnostic testing and clinical response are: (1) a prolonged clinical course and/or persistence of symptoms, i.e., 2 to 3 weeks or longer, (2) a history of no response, partial response, or relapse of symptoms after treatment with beta-lactam and/or sulphonamide-based antibiotics, (3) a "biphasic illness" presentation and (4) development of chronic respiratory sequelae such as persistent wheezing (asthma), chronic bronchitis or non-descript persistent URI-type symptoms (including sinus drainage) following acute illness. The important theory that chronic *C. pneumoniae* infection can cause persistent cardiopulmonary diseases has been discussed elsewhere.

What antibiotic treatment regimens are effective in managing acute non-pneumonic *C. pneumoniae* respiratory infections? The most widely recommended agents are macrolides and tetracyclines; clinical experience with quinolones is limited.

Beta-lactams may suppress chlamydial growth but are not cidal. Sulfonamide-based antibiotics, while effective against *C. trachomatis*, are ineffective against *C. pneumoniae*. Erythromycin base, if tolerated, is a useful agent although doxycycline may be better tolerated, especially if treatment is prolonged (see below). The new azalide azithromycin is also clinically effective.

At this time, choice between these newer agents should be based on tolerability, cost and convenience, since there are no published head-to-head comparisons of efficacy or effectiveness for any of the agents. Finally, it should be mentioned that persistent culture-positivity following clinical resolution of illness after any of these treatments seems to be common but the clinical implications of this observation remain to be completely delineated.

After choice of an antichlamydial antibiotic to treat an acute illness suspected to be caused by *C. pneumoniae*, what are the next most important considerations? In my opinion, the three next most important things to remember about antibiotic treatment of *C. pneumoniae* infection are *duration*, *duration*, and *duration*. Relapse of illness may follow conventional (7 to 10 day) courses of appropriate antibiotics, therefore longer courses (2 or three weeks) have been recommended. I will not hesitate to treat for three weeks (sometimes even longer) a persistent respiratory illness that I know or believe may be caused by *C. pneumoniae*. My motto in this era of antibiotic overuse for viral-type respiratory illnesses is "treat adequately, or not at all."

Conclusions

About 70% of acute *C. pneumoniae* infections are asymptomatic or produce minimal symptoms that do not trigger a medical encounter unless the symptoms are persistently bothersome. The remaining 30% of infections cause pneumonia or acute non-pneumonic respiratory syndromes, mainly bronchitis, pharyngitis/laryngitis, sinusitis, or otitis separately or in combination. In general, these illnesses are indistinguishable from those caused by respiratory viruses or other atypical organisms such as *Mycoplasma pneumoniae*. Therefore, widespread recognition of the importance of *C. pneumoniae* infection by practicing clinicians, including its diagnosis and therapy, must await the development and dissemination of rapid, reliable and inexpensive diagnostic tests for identification of this important respiratory pathogen.

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