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AFEBRILE PNEUMONIA IN INFANTS

Gregory P. DeMuri, MD

The syndrome of afebrile pneumonitis in infants is a relatively common disease that has gone by myriad names in the medical literature. Appellations for this clinical syndrome have included atypical pneumonia, infantile pneumonitis, interstitial pneumonia, viral pneumonia, or nonbacterial pneumonia. Despite this confusion of names, most clinicians are familiar with the clinical picture of a patient with a pneumonia that is not a typical lobar or lobular process as seen with pyogenic bacteria such as Streptococcus pneumoniae. For this article, afebrile pneumonia is defined as a pneumonitis with the following:

1. Acute or subacute onset
2. Lack of fever or low-grade fever (< 102°F)
3. Clinical signs suggestive of a pulmonary process such as cough, tachypnea, or mild to moderate respiratory distress
4. Infiltrates on chest radiographs such as perihilar or interstitial infiltrates
5. Lack of evidence of an acute pyogenic bacterial process such as a normal or only mildly elevated white blood cell count and no response to β-lactam antibiotics such as amoxicillin or cephalosporins.

This definition is intended to apply to the majority of children, but clearly there are exceptions. For instance, some infants with an atypical pneumonia present with fever. Terms that imply an etiologic agent such as nonbacterial pneumonia should be avoided because bacterial agents are actually common causes of afebrile pneumonia, as is discussed. This article focuses mainly on afebrile pneumonia in infants, in particular, those younger than 6 months of age. Comparison are made to pneumonia in older children. Etiologic agents are discussed as well as the clinical presentations, diagnosis, and treatment of afebrile pneumonia in infancy.

CAUSE AND CLINICAL MANIFESTATIONS

The causes of afebrile pneumonia in infancy are many. The following list describes agents that have been associated with this disease:

From the Divisions of General Pediatrics and Adolescent Medicine and Infectious Diseases, Department of Pediatrics, University of Wisconsin Medical School, Madison, Wisconsin
• Viruses
  Respiratory syncytial virus (RSV)
  Enteroviruses
  Parainfluenza
  Influenza
  Adenovirus
  Rhinovirus
  Coronavirus
  Herpes simplex* (HSV)
  Measles*
  Rubella*
  Varicella*
  Cytomegalovirus (CMV)
  Epstein-Barr*

• Bacteria
  Chlamydiae are bacteria that are obligate, intracellular parasites. Two species
  of Chlamydiae are well-known human pathogens: C. trachomatis (the agent of ure-
  thritis and cervicitis in adults and conjunctivitis and pneumonia in newborns) and
  C. psittaci (the agent of psittacosis, a zoonoses transmitted from birds). A third
  species, C. pneumoniae (formerly TWAR agent), recently has become well estab-
  lished as a common respiratory pathogen. This organism has been covered in
detail elsewhere in this issue and is mentioned briefly because it relates to lower
respiratory tract infection in infancy.

  The developmental cycle of chlamydiae involves two phases: the infectious
  form or elementary body and the noninfectious form but metabolically active re-
ticulate body. The elementary body is responsible for attachment to host cells,
which then engulf the organism. Fusion of membranes occurs, and the organism
is released, resulting in cytolysis.18 Pathologic features include interstitial pneu-
monia with a diffuse intra-alveolar mononuclear infiltrate with eosinophils. Focal

  *These agents are rare causes of afebrile pneumonia in infants, or the etiologic relation-
ship is controversial (see text).

Several series of patients hospitalized for pneumonia have implicated Chlamydia trachomatis, viruses, and even more unusual agents such as Pneumocystis and Ureaplasma. Most patients with afebrile pneumonia, however, are seen by a primary care provider in the outpatient setting, and large series of patients in this clinical setting are lacking. Nonetheless, important clinical information from these limited studies can be extrapolated to some extent. Each of the major causes of afebrile pneumonia is discussed.

Chlamydia trachomatis

Chlamydiae are bacteria that are obligate, intracellular parasites. Two species
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aggregates of neutrophils, lymphocytes, and plasma cells as well as atelectasis and mucous plugging also may be seen.\textsuperscript{17}

\textit{C. trachomatis} is the most common sexually transmitted diseases in adolescents and adults.\textsuperscript{20} It therefore can be expected that disease in newborns, acquired from the mother, should be relatively common. Transmission of the organism occurs during vaginal delivery to a mother infected with chlamydia. Infection after cesarean section is rare but can occur when amniotic membranes have been ruptured before delivery. The portals of entry and subsequent sites of infection are the eyes, nasopharynx, respiratory tract, and vagina of the infant. The estimated incidence of infants born with chlamydial infection is 8.2 to 35 per 1000 live births.\textsuperscript{20,37} The rate of transmission to an infant born to a mother infected with chlamydia is 50\% to 70\%, and of these infants, approximately 15\% develop pneumonia.\textsuperscript{18,20} Once transmitted, persistence of the organism may occur for as long as 3 years.\textsuperscript{19} This has profound implications for the diagnosis of sexual abuse of the child and is discussed elsewhere.\textsuperscript{18}

Infants with chlamydial pneumonia typically present between 3 and 16 weeks of age but may be seen as early as 2 weeks and as late as 4 months after delivery.\textsuperscript{18} The presentation is usually one of an afebrile child with a persistent staccato cough. Onset of cough is insidious, often during a period of several days to weeks. Nasal discharge may or may not be present. Physical examination reveals a mild to moderately ill infant; with tachypnea, rales, and perhaps wheezing on auscultation. Otitis media is present in more than one half of the cases, although the etiologic role of chlamydia in the middle ear is controversial.\textsuperscript{37} The presence of conjunctivitis in a newborn or young infant with pneumonia should alert the clinician to the possibility of chlamydial infection. Its absence, however, does not rule out \textit{Chlamydia} as a possible etiologic agent because concomitant conjunctivitis may be present only 50\% of the time.\textsuperscript{29} Signs of systemic illness typically are not present.

Examination of the peripheral blood shows a normal or mildly elevated white blood cell count with an absolute eosinophilia (> 300 cells/mm\textsuperscript{3}). Elevation of the total serum immunoglobulin G, M, and A (not specific to chlamydia) is described classically, although this has dubious diagnostic value. Radiographic findings are variable and may consist of hyperinflation or a diffuse, bilateral infiltrate. Infiltrates may be interstitial, reticular nodular, or coalescent\textsuperscript{20} (Fig. 1).

\begin{center}
\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Chest radiograph of an infant with \textit{C. trachomatis} pneumonia. Note the diffuse, bilateral infiltrates. (Courtesy of Mary Ellen Peters, MD.)}
\end{figure}
\end{center}
Viral Pneumonia

Viruses are the most common cause of pneumonia in children and certainly are responsible for the majority of cases of afebrile pneumonia. For example, Paisley et al. showed that 79% of pneumonia in infants younger than 1 month of age had a viral cause. Similar epidemiology has been found for older infants and children. The types of viruses that cause pneumonia vary with age, however:

- Infants younger than 1 month old*
  - RSV
  - Enterovirus
  - Rhinovirus
  - Adenovirus
  - Parainfluenza virus
  - HSV
- Children older than 1 month of age
  - RSV
  - Parainfluenza virus
  - Influenza virus
  - Adenovirus
  - Rhinovirus
  - Coronavirus

Infants younger than 1 month of age are more likely to be infected with RSV, enteroviruses, rhinovirus, adenovirus, and parainfluenza virus.

RSV is probably the most common cause of afebrile pneumonia in young infants. This virus causes upper respiratory tract infections, bronchiolitis, and pneumonia and has its peak onset between age 2 and 5 months. Its epidemic, seasonal occurrence in December through February is a phenomenon well known to practitioners who see children.

Parainfluenza is a respiratory virus that causes croup and other respiratory tract infections, including viral pneumonia. Its four serotypes are prevalent to varying degrees throughout the year. Influenza virus causes disease in epidemics in the winter months. Of three antigenic serotypes, types A and B cause the majority of disease. The virus is classified further by its hemaglutinin (H1, H2, H3) and neuraminidase (N1, N2) glycoprotein antigens on its surface. Hospitalization rates are as high as 0.5% in the first year of life for influenza lower respiratory tract disease.

Adenovirus is a frequent cause of rather severe pneumonia in infancy. It is stereotyped into 47 subgroups with types 1, 2, 3, 5, and 7 causing the majority of respiratory disease. Pneumonia and disseminated disease in newborns often results from perinatal transmission. Rhinoviruses are widespread causes of the common cold, but are implicated as causes of pneumonia in young infants as well.

Enteroviruses also may be frequent causes of pneumonia, particularly in the neonatal period. In fact, enteroviruses, rhinoviruses, and adenoviruses together make up 40% of the cases of newborn pneumonia in hospitalized patients. Other viruses such as CMV and HSV cause a minority of neonatal or infant pneumonia. In older infants and children, coronaviruses may cause pneumonia, particularly in those with underlying pulmonary disease such as asthma.

CMV is a well-known cause of disease in immunocompromised patients and in infants infected perinatally. Pneumonia is found in only 1% of newborns with congenital CMV syndrome. These infants usually have other manifestations of

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*Listed in decreasing order of frequency of isolation.
AFPRILE PNEUMONIA IN INFANTS

congenital CMV infection. Its role in nattably and postnatally acquired pneumonia in normal newborns is less clear. Stango et al's study found CMV in 21% of reportedly immunocompetent infants with pneumonia. On follow-up, however, many of these infants died of other infections that raised the question of an undetected immunodeficiency. Asymptomatic infection with this virus in the newborn period is common. Furthermore, in a retrospective review, Abzug reported no isolates of CMV in newborn infants with clinical pneumonia. The role of CMV in afebrile pneumonia in normal newborns appears to be controversial and probably minor.

Transmission of RSV and parainfluenza results mainly from contact with contaminated inanimate surfaces and hands. The other respiratory viruses are transmitted by small-particle aerosolization such as that which occurs with coughing and sneezing. Perinatal acquisition plays a role in the transmission of adenovirus, enteroviruses, CMV, and HSV. This may occur transplacentally, through contact with the infected contents of the birth canal or postnatally from contact with an infected parent.

Initial contact with the virus occurs in the eyes, nose, and mouth, leading to replication in epithelial cells. Ciliary loss, sloughing of mucosa, and stasis of mucus then ensues. Lower respiratory tract infection develops by local extension along the respiratory tree, usually resulting in one of four patterns of disease: acute bronchiolitis, necrotizing bronchiolitis, interstitial pneumonitis, or alveolar pneumonia. Of these, interstitial pneumonia and bronchiolitis are the most common. Host defense mechanisms against these respiratory viruses involve secretory and serum antibody responses. Cell-mediated immunity, particularly a cytotoxic T-cell response, is of importance as well. Of note is the uncanny ability of some respiratory viruses to develop a year-to-year antigenic change to evade host defenses. Influenza virus is the agent most well known for this phenomenon. Other viruses such as RSV are able to reinfect individuals throughout their life span, although it is usually the first infection that produces lower respiratory tract disease, with subsequent bouts of infection resulting in relatively minor illnesses.

Infants with viral pneumonia usually present following a 1-day to 2-day history of rhinorrhea and cough. Compared with chlamydial pneumonia, the onset of viral pneumonia is usually more rapid. Presenting symptoms may be relatively nonspecific, such as poor feeding, irritability, congestion, lethargy, cyanosis, or even apnea. Fever frequently is not present, especially in very young infants. In fact, 70% to 80% of infants younger than 1 month of age will present afebrile. Physical examination findings include tachypnea, rales on auscultation of the chest, and signs of respiratory distress such as retractions, nasal flaring, grunting, and cyanosis. Wheezing may be found when bronchiolitis also is present.

Because tachypnea is such a cardinal sign of pneumonia in infancy, a note regarding its definition is in order. This definition in young children has been somewhat controversial. A useful one adjusted to maximize the sensitivity and specificity of tachypnea as a sign of pneumonia in young children is as follows: infants younger than 6 months of age, respiratory rate greater than 60 breaths per minute, aged 6 to 11 months, greater than 50 breaths per minute, and 12 to 23 months greater than 40 per minute. The white blood cell count in children with viral pneumonia may be variable, ranging from normal to elevated with a predominance of neutrophils. Chest radiographs show most commonly interstitial infiltrates, lobar consolidation, peripheral infiltrates, atelectasis, or a combination of these findings. Complications from viral pneumonia overall are uncommon and usually occur in infants with underlying risk factors such as congenital heart disease, immunodeficiency, or chronic lung conditions. For instance, infants with bronchopulmonary dysplasia often are affected severely by viral infection with viruses.
such as RSV. These infants may be left with more chronic pulmonary compromise following such an infection.

Secondary bacterial infections are a well-known complication following influenza and parainfluenza disease, often associated with *S. aureus*, *S. pneumoniae*, or *H. influenzae*. Apnea is usual following RSV infection in children younger than 6 months of age. These infants may present with cyanotic spells that are usually self-limited, although distressing to caregivers. Mortality is uncommon, but these infants occasionally require short-term apnea monitoring. Other, more rare sequelae of viral pneumonia include bronchiolitis obliterans, adult respiratory distress syndrome, unilateral hyperlucent lung syndrome, chronic atelectasis, and pulmonary fibrosis. Asthma following viral respiratory tract infection is well described. Whether this is a consequence of RSV infection or that these children have an underlying predisposition to asthma remains an area of controversy. Overall, mortality of these infections is relatively low, given their frequency of occurrence. Adenovirus however, is particularly virulent early in infancy and may disseminate to visceral organs, resulting in death.

**Pneumocystis carinii**

*Pneumocystis carinii* is a pathogen previously defined as a protozoan, now believed to be more related to the fungi, based on DNA homology. Although typically found causing disease in immunocompromised individuals, this organism has been associated with afebrile pneumonia in normal infants.

Stango et al. studied 67 infants hospitalized for pneumonia in 1980. Of these children, 10 (14%) had evidence of *Pneumocystis* infection based on detection of circulating antigen and development of an antibody response not found in appropriate control patients. All of these patients (aged 2–12 weeks) presented afebrile and most had tachypnea or wheezing. Several presented with apnea. Radiographic findings included diffuse alveolar filling defect, air trapping, small, discrete peripheral nodules, and segmental atelectasis. There were suggestions that trimethoprim/sulfamethoxazole resulted in improvement, although these were uncontrolled observations. The infants in this series were generally quite ill, having been preselected as inpatients who were hospitalized for a median of 21 days. No immunologic abnormality was found in these infants, although one child died of infection at a later date. It is conceivable that the technical methods used to evaluate immunologic function may have missed significant abnormalities, although they were state of the art at the time of this study.

The question arises then, does *P. carinii* cause less severe forms of afebrile pneumonia in immunologically normal children? The answer to this question remains unknown, but a seroepidemiologic study reported in 1978 that 35% of normal infants develop antibody to *P. carinii* by 1 year of age and approximately 75% by 4 years of age. It is likely that these children developed asymptomatic infections or mild infections that went undiagnosed as having been caused by *Pneumocystis*.

With the emergence of HIV infection in the United States, there has been renewed interest in *P. carinii* as a cause of pneumonia in infants. *P. carinii* pneumonia is the most common opportunistic infection in children with perinatally acquired HIV infection. The peak time of presentation of these infants occurs between 2 and 6 months of age. These infants typically present with tachypnea, respiratory distress, hypoxia, and interstitial infiltrates on chest radiograph. Mortality is high even with antimicrobial therapy. Agents such as trimethoprim/sulfamethoxazole are used to prevent such disease in HIV-infected infants.
Ureaplasma and Mycoplasma hominis

Mycoplasma is a genus of bacteria that are the smallest free-living microorganisms in nature. Ureaplasma urealyticum and M. hominis are frequently inhabitants of the genital tract and may play a role in afebrile pneumonia of infancy. Their role as etiologic agents in this disease entity remains controversial. It is clear that these two species cause serious disease in neonates. Ureaplasmas have been associated with prematurity and with the development of chronic lung disease in infants of low birth weight. M. hominis and U. urealyticum have been linked to CNS infections as well in this population. Meningitis, intracranial hemorrhage, and hydrocephalus have been associated with the presence of these organisms in preterm neonates. Many of these infants have concomitant pneumonitis. Establishing evidence for an infectious role in normal, term newborns has been more difficult.

Stango et al. studied 104 infants between 2 and 12 weeks of age with pneumonia. These infants presented with tachypnea, cough, retractions, rales, and infiltrates on chest radiograph. Most were afebrile. The authors found that 21% of patients with pneumonia had U. urealyticum cultured from the nasopharynx, compared with 4% of controls. None were positive for M. hominis. There are several difficulties in concluding from this data that Ureaplasmas are an etiologic agent in pneumonia. First, the presence of the microorganism in the nasopharynx does not correlate necessarily with lower respiratory tract infection. Second, six of eight patients with Ureaplasma isolated had other significant pathogens such as CMV, C. trachomatis, and B. pertussis found concomitantly.

A prospective study by Syrogionnopoulos et al. shed further doubt on this hypothesis. This study involved infants who were colonized with Ureaplasma shortly after birth. The authors found that lower respiratory tract infection developed in 5 of 51 colonized infants and 9 of 57 uncolonized infants. They concluded that there is no increased risk for lower respiratory tract infection in infants colonized with U. urealyticum, although the power of the study to detect such a risk was not addressed. The role for Ureaplasma in afebrile pneumonia remains dubious. These children are not usually ill enough to warrant a definitive tissue diagnosis, although isolation from lung tissue and amniotic fluid has been reported. Molecular techniques such as the polymerase chain reaction may help to shed additional light on this problem.

Other Agents

Despite widespread immunization, B. pertussis continues to be a too frequent cause of respiratory illness, including pneumonia in young children. These afebrile infants present with a 1-week to 2-week history of rhinorrhea and cough, known as the catarrhal stage. This is followed by the paroxysmal stage in which bouts of severe cough and the classic inspiratory whoop are observed. Vomiting after such an attack is common. Infants younger than 6 months may present with apnea, and in this age group the characteristic whoop is frequently absent. The convalescent stage of illness follows, with cough persisting for as long as several months. Recurrence of the cough with subsequent respiratory infections is not infrequent.

Complications of pertussis include seizures, hypoxic encephalopathy, and apnea. Physical examination usually is relatively normal, although occasionally rales or rhonchi may be heard. The white blood cell count shows a characteristic lymphocytosis, although in young infants this response may be lacking and the white blood cell count may be normal. Chest radiograph shows perihilar infiltrates (the shaggy heart), lobar infiltrates, or atelectasis. Pertussis should be considered even
in immunized infants. Recent reports suggest that the efficacy of whole-cell pertussis vaccines is much lower than expected.\textsuperscript{13,16} 

\textit{C. pneumoniae} is a relatively newly recognized respiratory tract pathogen in older children and adolescents and a common cause of afebrile pneumonia in this population. Two large population-based studies, one in Seattle\textsuperscript{3} and one in Spain,\textsuperscript{25} failed to detect any serologic evidence of previous infection with \textit{C. pneumoniae} in children younger than 2 years. Furthermore, Yeung et al\textsuperscript{38} specifically looked for serologic evidence of this agent in infants with lower respiratory tract infection and found none. Infection in a neonate\textsuperscript{22} and an 11-month-old child\textsuperscript{22} have been reported, but it is clear that \textit{C. pneumoniae} is a rare cause of pneumonia in infancy.

\textit{M. pneumoniae} is also a frequent cause of afebrile pneumonia in children aged 5 and older. Like \textit{C. pneumoniae}, \textit{M. pneumoniae} is a much less frequent cause of pneumonia in infancy. Although some seroepidemiologic studies have shown antibody to \textit{Mycoplasma} in 28\% to 40\% of children younger than 1 year of age,\textsuperscript{7} a prospective study of infants in a daycare center indicated that most infants who are culture positive for \textit{Mycoplasma} are asymptomatic.\textsuperscript{12} Infants who present with pneumonia in the first several months of life therefore are unlikely to be infected with \textit{M. pneumoniae}.\textsuperscript{32} This may be in part because of passively transferred, protective maternal antibodies.

\section*{DIAGNOSIS}

The diagnosis of afebrile pneumonia is a clinical one based on criteria delineated earlier. Chest radiographs provide additional evidence for pulmonary disease in the correct clinical setting. Findings on chest radiographs are variable and may include hyperinflation, perihilar infiltrates, patchy consolidation, atelectasis, interstitial infiltrates, alveolar defects, or even a nodular appearance (see Fig. 1). Chest radiographs have been shown to have poor sensitivity and specificity in the differentiation of typical bacterial pneumonia from nonbacterial pneumonia, even when combined with clinical information.\textsuperscript{10}

Methods for determining the cause of afebrile pneumonia are commonly available and are listed in Table 1. For \textit{C. trachomatis}, isolation of the organism by

\begin{table}
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\caption{METHODS FOR ESTABLISHING THE CAUSE OF AFEBRILE PNEUMONIA IN INFANCY}
\begin{tabular}{|l|c|c|c|}
\hline
\textbf{Causative Agent} & \textbf{Serology} & \textbf{Culture} & \textbf{Other} \\
\hline
\textit{C. trachomatis} & $-$ & $+$ & EIA, DFA, DNA probe, PCR \\
RSV & $-$ & $+$ & EIA, DFA \\
Influenza virus & $+$ & $+$ & EIA, DFA \\
Parainfluenza virus & $+$ & $+$ & EIA, DFA \\
Adenovirus & $+$ & $+$ & EIA, DFA \\
Rhinovirus & $-$ & $+/-$ & \\
Coronavirus & $-$ & $-$ & \\
Enteroviruses & $+$ & $+$ & \\
P. carinii & $-$ & $-$ & BAL biopsy \\
\textit{M. hominis/Ureaplasma} & $-$ & $+$ & \\
\textit{M. pneumoniae} & $+$ & $+$ & \\
\textit{Ch. pneumoniae} & $+$ & $+$ & \\
\textit{B. pertussis} & $-$ & $+$ & \\
\hline
\end{tabular}
\end{table}

\textit{RSV} = respiratory syncytial virus; \textit{EIA} = enzyme immunoassay; \textit{DFA} = direct fluorescent antibody; \textit{PCR} = polymerase chain reaction; \textit{BAL} = bronchoalveolar lavage.
culture from eyes, nasopharynx, or rectum is considered the gold standard. Rapid techniques such as enzyme immunoassay and direct fluorescent antibody are approved for conjunctivitis and are sensitive and specific. Molecular techniques such as DNA probe and polymerase chain reaction are not approved for use in children but may be of some value. If chlamydial pneumonia is suspected clinically, a swab of the nasopharynx should be obtained for chlamydia direct fluorescent antibody and chlamydia culture. Direct fluorescent antibody results are usually available in 1 day, and culture within 3 to 4 days. If conjunctivitis is present a swab of the conjunctiva should be obtained and sent for direct fluorescent antibody and culture. Swabs for chlamydia culture must be placed in transport media and delivered promptly to the laboratory because chlamydia are fastidious and killed easily.

The diagnosis of viral pneumonia can be made using tissue culture methods or rapid antigen techniques. RSV, parainfluenza, and influenza take between 3 and 5 days, with adenovirus requiring up to 10 days for isolation by culture. Rapid antigen techniques can provide an answer in a matter of hours and are available for RSV, influenza, parainfluenza, and adenovirus. Sensitivity ranges from 60% to 90% for RSV to as low as 22% for adenovirus. Availability of these tests is variable from institution to institution. Rhinovirus and coronavirus are difficult to isolate in culture and serologic testing is not readily available. Enteroviruses may be cultured or identified by serologic response.

Pneumocystis pneumonia is difficult to diagnose without biopsy or bronchioaveolar lavage. This usually is reserved for infants that have a degree of illness and clinical course that would warrant such invasive procedures. Serologic diagnosis and antigen detection of P. carinii are experimental and not widely available. M. hominis and Ureaplasma are identified by culture of nasopharyngeal material. A positive culture may be incidental and does not prove an etiologic role in the pneumonia. M. pneumoniae can be associated with a positive, cold agglutinin response, although this is nonspecific. M. pneumoniae and C. pneumoniae are confirmed by IgM or IgG specific serology. Both agents may be isolated in tissue culture from respiratory tract specimens such as a nasopharyngeal swab.

Given the expense, delay in receiving results, need to institute treatment early, and usual mild degree of illness, the majority of infants with afebrile pneumonia do not require most of the aforementioned diagnostic techniques to identify a specific etiologic agent. A few situations in particular would warrant such an evaluation. The first is an infant with a clinical course compatible with C. trachomatis pneumonia, namely an infant 3 to 16 weeks of age, afebrile with a staccato cough, with or without conjunctivitis. Diagnosis of Chlamydia in these infants necessitates investigation and treatment of the mother and her sex partners according to Center for Disease Control and Prevention guidelines. Normal infants who have a rather severe degree of illness or infants who have an underlying condition such as an immunodeficiency warrant a thorough search for an etiologic agent. Investigation of infants may be warranted during a community outbreak such as an influenza epidemic. Knowledge of the causative agent in these instances may suggest a specific useful therapy or obviate the use of ineffective therapeutic agents.

THERAPY AND PREVENTION

At the time the clinician is faced with an infant with afebrile pneumonia, the etiologic agent is not known and one must decide whether to treat the child empirically. There are several practical considerations that must be considered when making this decision: (1) establishing an etiologic diagnosis is difficult and may
take days to weeks, at which point the patient may have recovered from the illness and would benefit little from the diagnosis; (2) establishing a cause is expensive, requiring multiple diagnostic tests, the cost of which markedly exceed an empiric course of antibiotics; (3) a large percentage of these cases have a viral cause, and these patients will not benefit from antibiotics, but distinguishing bacterial from viral disease on clinical grounds is often difficult; and (4) treatment is most effective when instituted early in disease, especially for agents such as Chlamydia and Mycoplasma.

A reasonable approach then, when faced with the infant whose clinical picture suggests afebrile pneumonia and radiographic findings are compatible with this diagnosis, is to institute therapy with erythromycin, 40 to 50 mg/kg/d in four divided doses for 10 days. A course of 14 days is recommended if C. trachomatis or B. pertussis is diagnosed or highly suspected. The spectrum of erythromycin includes Chlamydia, Mycoplasma, S. pneumoniae, Staphylococcus, Ureaplasma, and B. pertussis. If otitis media also is present, the combination drug erythromycin/sulfasoxazole will provide additional action against the otitis media pathogens H. influenzae and M. catarrhalis. The newer macrolides clarithromycin and azithromycin have an in-vitro spectrum that spans all the above. These agents are available in suspension form and are approved for the treatment of otitis media. They are not approved for the treatment of pneumonia in infancy but should be effective and offer an attractive alternative for the patient with gastrointestinal intolerance to erythromycin.

Specific antiviral therapy is used only in certain circumstances. Ribavirin for treatment of RSV lower respiratory tract disease may be considered for infants with underlying conditions such as congenital heart disease, bronchopulmonary dysplasia, other chronic lung disease, or immunocompromise. Amantidine and rimantidine are antiviral agents with activity against influenza virus. They are not approved for use in infants.

Prevention of afebrile pneumonia involves preventing infection with the multitude of agents discussed. Preventing pneumonia from C. trachomatis involves testing and treating the mother and her partners during the pregnancy. Vaccination for influenza is recommended for children with underlying heart or lung disease, or with chronic diseases such as asthma, diabetes, or sickle-cell anemia. It is not recommended for infants younger than 6 months of age. Immunization against B. pertussis should be a routine part of well child care for all children, starting at 2 months of age. Great strides in preventing this illness will be made when vaccines that prevent infection with respiratory viruses are available for use in this age group.

CONCLUSION

Afebrile pneumonia in early infancy is a common problem faced by any practitioner who sees children. These infants present usually without fever and with infiltrates on chest radiography in a variety of patterns. Respiratory viruses are the most common agents of this clinical syndrome, followed in frequency by C. trachomatis and B. pertussis. Unlike older children, newborns and infants younger than 6 months of age rarely are affected by C. pneumoniae or M. pneumoniae. Agents such as Pneumocystis and Ureaplasma historically have been implicated as playing a role in this disease in normal infants. Conclusive evidence confirming such a role is lacking, however.

Diagnosis of the cause of afebrile pneumonia is useful when chlamydia or another bacterial agent is suspected and relies on a variety of rapid antigen and culture techniques. Therapy with erythromycin will benefit those infants with a
infection caused by the common nonviral agents that cause pneumonia in this age group. Immunization of infants and detection and treatment of chlamydia in pregnant woman are important in prevention of disease in infancy.

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Address reprint requests to Gregory P. DeMuri, MD Department of Pediatrics University of Wisconsin Medical School 600 Highland Avenue H6/440 Madison, WI 53792-4116