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Pneumonia in Children and Adolescents

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Epidemiology

Lower respiratory infections, including pneumonia, are the leading infectious cause of death worldwide, accounting for 4.3 million deaths annually (Murray & Lopez, 1997). As a cause of death, such infections are overrepresented in children and in those in developing countries. In developing countries, the incidence of pneumonia varies from 21 to 296 episodes per 100 child-years (Selwyn & Board on Science and Technology for International Development of the National Research Council [BOSTID], 1990). The rates are at least an order of magnitude less in industrialized countries. For example, in North America, the incidence ranges from 30 to 35 episodes per 1000 children less than 5 years of age to 6 to 12 episodes per 1000 in older children and adolescents (Alexander et al., 1966; Foy et al., 1973; Murphy et al., 1981: Wright et al., 1989).

Studies of pneumonia have been hampered by the lack of an accepted standard for its diagnosis and the inability to obtain direct specimens for etiologic diagnosis. Furthermore, most studies have been conducted in hospitalized children. Thus, the literature on etiology, appropriate management, and prognosis relating to this syndrome must be interpreted with caution.

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Risk factors that increase the incidence or severity of pediatric pneumonia include prematurity, malnutrition, low socioeconomic status, passive exposure to cigarette smoke, and attendance at day care centers (Wang & Law, 1998). Underlying diseases, especially those affecting the cardiopulmonary, immune, or nervous systems, also increase the risk for developing severe pneumonia (Adler-Shohet & Lieberman, 1998; Wang & Law, 1998).

Etiologic Agents

Aside from one U.S. study (Rapkin, 1975), all studies that have obtained direct lung specimens for etiologic diagnosis have been conducted in developing countries (Vuori & Peltola, 1998). The dearth of these investigations in industrialized countries is presumably because obtaining such specimens is considered inordinately invasive for a condition that usually responds to empiric therapy. Thus, most etiologic diagnoses have been based on indirect methods of diagnosis. These methods can be grouped into two categories: (1) recovery of organisms from the upper respiratory tract, inferring that they are responsible for the lower tract symptomatology, and (2) recovery of organisms from another site, such as blood, in a patient with pneumonia, with serologic assays demonstrating either antigens or an increase in antibodies. As these methodologies have been developed in different centers, the spectrum of infectious agents has changed accordingly (Isaacs, 1989). These methods have been used without direct comparison with pulmonary speci-

mens and, in many investigations, without adequate controls. Even in such research settings, etiologies are identified in only 40% to 60% of cases (Claesson et al., 1989; Davies et al., 1996a; Heiskanen-Kosma et al., 1998; Hietala et al., 1989; Isaacs, 1989; Korppi et al., 1993a; Nohynek et al., 1991; Paisley et al., 1984; Ruuskanen et al., 1992; Turner et al., 1987).

The recovery of pyogenic bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae* from the upper respiratory tract is not sufficient evidence to identify the causative pneumonia pathogen because these bacteria are frequent colonizers of the upper respiratory tract. However, because the majority of lower respiratory infections occur after aspiration of upper tract organisms, recovery of an organism that is not an upper tract colonizer may be more predictive of the lower tract pathogen.

Recognizing these pitfalls in determining etiologies, a number of generalities can be made because they have been found consistently across different studies. The greatest indicator of the causative pathogen is the age of the child (Table 1). Vertical transmission of organisms from the maternal genital tract is the main route of entry of pathogens in the neonatal and early infancy period. Infection with group B streptococci, *Listeria monocytogenes,* and gram-negative bacilli produces a septic picture that includes pneumonitis presenting soon after birth and associated with risk factors such as preterm labor, prolonged rupture of membranes, and maternal fever (Adler-Shohet & Lieberman, 1998). This presentation usually occurs within hours or days of birth. Afebrile pneumonitis syndrome with an insidious presentation in the first 3 months of life is seen with *Chlamydia trachomatis* pneumonia (Beem & Saxon, 1977; Harrison et al., 1978; Tipple et al., 1979). Although one early case series also found *Ureaplasma urealyticum,* cytomegalovirus, and *Pneumocystis carinii* to be responsible for this syndrome (Stagno et al., 1981), a more recent controlled study found *C. trachomatis* to be the only pathogen associated with this syndrome (Davies et al., 1996a).

TABLE 1. Age-Specific Causes of Pneumonia in Otherwise Healthy Children[a]

Age group	Pathogen (in order of frequency)
Neonate	Sepsis presentation. Group B streptococci, *Escherichia coli, Listeria monocytogenes*
1–3 months	Pneumonitis syndrome usually afebrile. *Chlamydia trachomatis*, respiratory syncytial virus, other respiratory viruses
4 months–5 years	Respiratory viruses, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*
6–18 years	*M. pneumoniae*, *S. pneumoniae*, *C. pneumoniae*, nontypeable *H. influenzae*, influenza viruses A and B, adenovirus, other respiratory viruses.

During the first 2 years of life, viruses are the most frequently implicated pathogens accounting for as much as 90% of pneumonias (Alexander et al., 1966; Denny & Clyde, 1986; Foy et al., 1973; Murphy et al., 1981; Wright et al., 1989). These include respiratory syncytial virus, parainfluenza virus types 1 to 3, influenza virus types A and B, adenovirus, herpes simplex virus, rhinoviruses, and enteroviruses (Henrickson, 1998). With increasing age and as the incidence of pneumonia decreases, bacterial pathogens including *S. pneumoniae, Mycoplasma pneumoniae,* and *Chlamydia pneumoniae* are more frequently implicated. By school age, only half of pneumonia cases are viral in origin (Denny & Clyde, 1986). A recent Finnish population-based serologic study found that *M. pneumoniae* was the second most common agent after *S. pneumoniae* in pneumonia infections in a school-age group and the most common pathogen in young adolescents, associated with half the cases (Heiskanen-Kosma et al., 1998). *C. pneumoniae* was the second most common agent after *M. pneumoniae* in young adolescents and was associated with one third of all pneumonia cases in that age group (Heiskanen-Kosma et al., 1998).

Clinical Findings

In the neonatal period, symptoms of pneumonia are usually secondary to the general manifestations of sepsis characterized by hypotonia, lethargy, apnea, floppiness, inability to maintain a normal body temperature, and hypotension (Adler-Shohet & Lieberman, 1998). The chest infection may be manifested by tachypnea and hypoxia, progressing

to apnea and a need for ventilatory support. Radiographic findings include discrete infiltrates or a diffuse reticulonodular pattern indistinguishable from the findings seen with hyaline membrane disease. This presentation is common to infection with all neonatal pyogenic pathogens.

A specific syndrome, the infant pneumonitis syndrome, has been well described with C. *trachomatis.* It typically occurs during the first to the third month of life with a repetitive staccato cough, tachypnea, progressive respiratory distress, and radiologic evidence of bilateral pulmonary infiltrates and air trapping (Beem & Saxon, 1977; Harrison et al., 1978; Tipple et al., 1979). The infant is usually afebrile. Chest examination may indicate diffuse crackles, but no wheezing. The patient is typically not as sick as the diffuse auscultatory and radiographic findings would suggest. Conjunctivitis is seen in half the cases. Other features include an elevated total IgM and eosinophilia.

The classic presentation of bacterial pneumonia has been described as a patient with a productive cough accompanied by abrupt onset of chills and rigors. Clinical assessment reveals decreased breath sounds and crackles, typically confined to one lobe. Lobar involvement can be confirmed on radiographic examination. The presentation of atypical pneumonia has been described as a nonproductive cough and low-grade fever, without the degree of toxicity that is seen with bacterial pneumonia. The radiograph seen with this syndrome typically shows more diffuse involvement. Although the classic presentation was thought to be indicative of infection by pathogens such as *S. pneumoniae* and *H. influenzae,* and the second presentation suggestive of infection by atypical agents such as *M. pneumoniae* and *C. pneumoniae,* it is now established that all pathogens may present in either way or along the spectrum between these two extremes (Fang et al., 1990). *Legionella pneumophila,* an important cause of community-acquired pneumonia in adults (Fang et al., 1990) is rarely seen in children who are not immunocompromised (Brady, 1989). Furthermore, in children, productive cough is distinctly uncommon and its sudden onset should suggest tuberculosis or cystic fibrosis.

In the adolescent presenting with cough and fever, reactivation tuberculosis should be considered as a possible diagnosis. Clues to this diagnosis include residence in a tuberculosis-endemic area or contact with individuals at high risk for tuberculosis such as aboriginal people, the urban homeless, incarcerated individuals, and those with HIV infection. A high prevalence of tuberculosis is found around the world including Asia, Africa, Latin America, and Eastern Europe. The illness may be subacute, lasting days to weeks, and may be associated with anorexia, weight loss, and night sweats (Starke & Correa, 1995). Sputum production and hemoptysis also differentiate tuberculosis from *C. pneumoniae* or *M. pneumoniae* infections.

Other aspects of a patient's epidemiologic history may be helpful in the diagnosis. For example, exposure to parrots or other psittacine birds is a clue to *C. psittaci* infection. Exposure to parturient farm animals such as sheep, goats, cattle, and cats raises the possibility of infection with *Coxiella burnetii.* Travel to or residence in certain areas may also be suggestive of fungal pulmonary infections. For example, *Coccidioides immitis* is endemic to southwestern United States, northern Mexico, and parts of Central and South America. *Histoplasma capsulatum* infection occurs in eastern and central United States and Canada. The presence of certain extrapulmonary findings such as erythema multiforme or joint manifestations is indicative *of M. pneumoniae* infection (Denny et al., 1971).

The accuracy of clinical criteria developed by the World Health Organization (WHO) for the diagnosis of pneumonia (WHO, 1984) in children presenting with fever and cough has been studied in industrialized countries (Table 2) (Berman et al., 1991; Grossman & Caplan, 1988; Leventhal, 1982; Taylor et al., 1995; Zukin et al., 1986). Using the presence of radiographically confirmed pneumonia as the gold standard, tachypnea—defined as >40 breaths per minute in children and >50 breaths per minute in infants—was found to be the most sensitive single indicator, with a sensitivity that ranged from 50% to 81% (Leventhal, 1982; Zukin et al., 1986). Respiratory rate may vary by the measurement method and the child's emotional state. Thus, the optimal assessment method is to count the rate by observation for a full 60 seconds with the child awake and not crying (Berman et al., 1991).

Although the presence of crackles was highly specific, it was not present in up to 57% percent of cases. Overall, no single sign was adequately sensi-

TABLE 2. Sensitivity and Specificity of Clinical Findings in Pediatric Patients with Radiographic Pneumonia[a]

	Berman et al., 1991	Leventhal, 1982	Zukin et al., 1986	Grossman & Caplan, 1988	Taylor et al., 1995
Number of patients	90	133	125	155	576
Number of pneumonia patients	63	26	18	51	42
Age range	<4 months	3 months–15 years	<17 years	<19 years	<2 years
Appearance					
Sensitivity (%)		92		67	
Specificity (%)		15		40	
Tachypnea					
Sensitivity (%)	62	81	50	64	75
Specificity (%)	63	60	68	54	70
Retractions					
Sensitivity (%)		35	17		
Specificity (%)		82	84		
Crackles					
Sensitivity (%)		44	57	43	
Specificity (%)		80	75	77	

[a]Adapted from Jadavji et al., 1997.

tive and specific to be used alone in diagnosing the presence or absence of pneumonia. One study found that all pneumonia cases had at least one of the following: respiratory distress, tachypnea, crackles, and decreased breath sounds (Leventhal, 1982). Thus, the *absence of all* four findings could be used to rule out pneumonia without need for a chest film. Measurement of tachypnea has good reproducibility compared with other findings such as detection of retractions, crackles, or wheezes (Godfrey et al., 1969; Wang et al., 1992, 1996). The accurate measurement of respiratory rate should be an integral part of the assessment of any child with suspected pneumonia.

Oxygenation status is a good predictor of disease severity associated with lower respiratory infection as measured by hospitalization duration (Hall et al., 1979; Shann et al., 1989; Simpson & Flenley, 1967). Cyanosis indicates severe hypoxia, but is usually absent in children with hypoxia (Simpson & Flenley, 1967). A normal general appearance and ability for the child to be consoled is a good indication of normal oxygenation (Margolis et al., 1994), but oximetry should be performed when hypoxia is a possibility, especially in a hospitalized child.

Diagnosis

Radiographs

Radiographic confirmation of the clinical diagnosis of pneumonia is necessary given the lack of agreement between clinical and radiologically confirmed pneumonia (Davies et al., 1996b; Redd et al., 1994). The entity of bronchitis, a viral infection, may present with similar findings but without demonstration of pulmonary infiltrates. Antibiotics are not indicated for this syndrome (O'Brien et al., 1998). The concern about overuse of antibiotics where they are not indicated is particularly cogent during this era of rising antibiotic resistance among the common community-acquired bacterial pathogens (Speert, 1996).

Radiographs provide an estimate of the extent of lung involvement and provide some clues to etiology. However, as with the clinical assessment, there is overlap of etiology with different radiographic findings (Bettenay et al., 1988; Isaacs, 1989; McCarthy et al., 1981), and radiographs can only provide guidelines as to etiology. Peribronchial thickening and diffuse interstitial infiltrates, particularly with hyperinflation, are associated with viral

infections, whereas lobar infiltrates and pneumatoceles are more suggestive of bacterial pneumonias (Korppi et al., 1993b; Redd et al., 1994). The finding of pleural effusions is more suggestive of pyogenic pneumonia (Asmar et al., 1978; Bartlett & Finegold, 1974; Chartrand & McCracken, 1982; Light et al., 1980) than of pneumonias due to *M. pneumoniae* or viruses (Fine et al., 1970). When effusions are seen with the latter infections, the amounts are much smaller (Fine et al., 1970).

The presence of hilar adenopathy on the chest radiograph suggests tuberculosis or pulmonary fungal infection, such as histoplasmosis or blastomycosis.

Routine follow-up films are not indicated unless the child has had recurrent pneumonias. In such situations, the follow-up films are helpful in determining whether there has been resolution between episodes (Wald, 1990).

Other Diagnostic Tests

The extent of investigation is tailored to the setting, the host, and the severity of illness. Thus, patients with mild to moderate illness can be managed expectantly without specific tests since empiric management is generally successful. A more aggressive investigative approach is indicated in those who have persistent or worsening symptoms, those who have underlying illness, or those who have severe disease. Infections for which treatment is different from empiric regimens should have priority. Studies that provide results in a timely manner relative to management decisions are helpful. Thus, only a few serologic assays are generally helpful, because many require the observation of a 4-fold rise in the convalescent titer taken 2 to 4 weeks after an acute serum sample is obtained.

Antigen detection of respiratory viruses allows rapid diagnosis, which may help provide specific treatment, including limiting unnecessary antibiotics, cohorting (Isaacs et al., 1991; Krasinski et al., 1990), and reducing unnecessary investigations. Such methods are available for detection of respiratory syncytial virus, parainfluenza viruses, influenza viruses, and adenoviruses (Hierholzer et al., 1989; Johnston & Bloy, 1993; Salomon et al., 1989; Thiele et al., 1989), but the sensitivity of these assays is limited by the availability and quality of the antisera used in either the enzyme immunoassay (EIA) or fluorescent assay. Compared with viral isolation, sensitivity of antigen detection for adenovirus is lowest, at about 20% compared with an average of 75% for other viruses (Henrickson, 1998).

Assays based on the polymerase chain reaction (PCR) have been combined into multiplex assays to detect different respiratory viruses (Henrickson, 1998). These methods are more sensitive than antigen detection assays, but the specificity of these assays needs improvement. These assays have also been developed for coronaviruses and rhinoviruses, which are difficult to grow on tissue culture (Pitkaranta et al., 1998). Their role in diagnosing the cause of pediatric pneumonia remains to be determined. The role of PCR in detecting *M. pneumoniae, C. pneumoniae,* and other organisms that do not normally colonize the upper respiratory tract is also being actively investigated.

Blood cultures should be performed in febrile patients with pneumonia since isolation of an organism provides proof of etiology. However, organisms are isolated in 10% to 30% of cases at most. When there is a pleural effusion, this fluid should be obtained for diagnostic as well as therapeutic reasons. In addition to cell count and biochemical tests, bacteriologic examination should be performed on the fluid. Gram's stain and aerobic and anaerobic culture for pyogenic organisms should be performed on all specimens, as this may be the only source of such an isolate. Etiologic agents are identified in up to 60% of empyemas (Cham et al., 1993; de la Rocha, 1982; Fajardo & Chang, 1987; Hoff et al., 1991). Where indicated, *M. tuberculosis* and fungal pathogens should also be sought, but pleural biopsy may have a better diagnostic yield (Boutin et al., 1990).

Serodiagnosis is the mainstay of diagnosis of *C. trachomatis* since infection by vertical transmission usually has occurred several weeks prior to onset of symptoms. Because of placental transmission of antibody to *C. trachomatis,* IgM-specific assays are confirmatory (Schachter, 1980). Serology may also be helpful in the diagnosis of *C. burnetii* (Sawyer et al., 1987) and *C. psittaci* infection. The role of *C. pneumoniae* serodiagnosis using microimmunofluorescence is controversial since the organism may be isolated in those who do

not demonstrate seropositivity (Hammerschlag, 1995). Neither method is widely available. Most serologic assays for respiratory viral diagnosis are of limited value because they are based on complement fixation (CF) methods, which are relatively insensitive particularly in young children with such infections. Serologic assays for *M. pneumoniae* using either CF or EIA methods may be helpful, but only retrospectively, because increases in antibody may only occur weeks after onset of illness (Kenny et al., 1990). The organism may be recovered from throat cultures, but this is performed only in research laboratories and may also take weeks to complete (Kenny et al., 1990). Serologic assays for antibody responses to pneumococcal antigens and pneumococcal immune complex assays have been used mainly in Finland (Heiskanen-Kosma et al., 1998).

When tuberculosis is suspected, skin testing with 5 Tuberculin units and culture of sputum or other respiratory specimen and gastric aspirates is indicated. The latter appears to be superior to a respiratory specimen in the pediatric patient with primary disease (Vallejo et al., 1994).

Management

General Management

Decisions about hospitalization of pneumonia patients must be individualized. Factors to consider include hydration status, oxygenation status, toxic appearance, lack of response to oral therapy, recurrence, or underlying disease. Parenteral hydration and antibiotics should be administered if oral intake is inadequate. Oxygen supplementation should be provided if patients are hypoxic. This should be specifically ruled out in patients who are hospitalized, and oxygenation status should be monitored until the patients are no longer hypoxic. Work of breathing should also be monitored and consideration given to positive airway pressure or ventilation in children who are "tiring out."

Three trials of vitamin A for the treatment of non-measles pneumonia have not found this intervention to be of benefit (Dowell et al., 1996; Kjolhede et al., 1995; Nacul et al., 1998). Thus, the addition of vitamin A is not indicated in the usual management of pneumonia.

Antimicrobial Treatment

Recommendations about the appropriate use of antimicrobials are limited by the dearth of randomized trials comparing drug efficacy. Thus, the antibiotic recommendations summarized in Table 3 are based on distribution of agents and their susceptibility most likely observed in different age groups.

Randomized trials conducted in adults with pulmonary tuberculosis have demonstrated the efficacy of 6-month regimens of combination isoniazid, rifampin, and pyrazinamide for 2 months followed by 4 additional months of treatment with the first 2 agents for susceptible tuberculosis (Combs et al., 1990; Snider et al., 1984). Twice-weekly therapy has been shown to reduce relapse rates from 21% to 6% and drug resistance from 14% to 2% through increased patient compliance (Weis et al., 1994).

Although randomized trials of ribavirin treatment of respiratory syncytial virus disease have been conducted, they have not been optimally designed, and a meta-analysis of their results concluded that further studies were needed to demonstrate efficacy (Randolph & Wang, 1996).

The choice of antibiotics in the early neonatal period reflects recommendations for the treatment of neonatal sepsis. Because of the high frequency of *C. trachomatis* in the afebrile pneumonia syndrome of infancy, a macrolide remains the treatment of choice (Beem et al., 1979). In those with more severe disease who are admitted to the intensive care unit, coverage is expanded to ensure efficacy against *S. aureus* and *H. influenzae* (Asmar et al., 1978; Chartrand & McCracken, 1982).

In those less than 5 years of age, *S. pneumoniae* is the most frequent bacterial organism. Unlike the case with pneumococcal meningitis, pneumonias due to penicillin-resistant *S. pneumoniae* continue to respond to penicillins and first- and second-generation cephalosporins (Bradley et al., 1995; Pallares et al., 1995). In a multicenter, retrospective study involving 254 children with pneumonia, Tan and colleagues (1998) compared the clinical characteristics of those with penicillin-susceptible and

TABLE 3. Empiric Antimicrobial Therapy for Pediatric Pneumonia, by Age Group

Age group	Outpatients	Patients in hospital	Patients in intensive care unit
1–3 months (afebrile pneumonitis)	Initial outpatient management not recommended	Erythromycin 40 mg/kg/d in four doses or other macrolide for 10–14 days	Erythrymycin 40 mg/kg/d in four doses or other macrolide for 10–14 days
1–3 months	Initial outpatient management not recommended	Cefuroxime 150 mg/kg/d in three doses for 10–14 days	Cefuroxime 150 mg/kg/d in three doses *or* cefotaxime 200 mg/kg/d in three doses *plus* cloxacillin 100–200 mg/kg/d in four doses for 10–14 days
3 months–5 years	Amoxicillin 40 mg/kg/d in three doses *or* erythromycin 40 mg/kg/d four doses *or* other macrolide for 7–10 days	Ampicillin 150 mg/kg/d in four doses *or* cefuroxime 150 mg/kg/d in three doses for 7–10 days	Cefuroxime 150 mg/kg/d in three doses *plus* erythromycin 40 mg/kg/d in four doses or other macrolide for 7–10 days
5–18 years	Erythromycin 40 mg/kg/d in four doses or other macrolide for 7 days	Erythromycin 40 mg/kg/d in four doses or other macrolide with or without cefuroxime 150 mg/kg/d in three doses or ampicillin 150 mg/kg/d in four doses for 7–10 days	Cefuroxime 150 mg/kg/d in three doses for 7–10 days, *plus* erythromycin 40 mg/kg/d in four doses or other macrolide for 7 days

[a]Adapted from Jadavji et al., 1997.

penicillin-nonsusceptible *S. pneumoniae.* Of the 257 pneumonia episodes occurring in these 254 children, 9% were of intermediate resistance and 6% were fully resistant to penicillin. No differences could be found in the clinical presentation of the children with susceptible and nonsusceptible disease. Although there was high variability in the choice of antibiotics, including parenteral and oral β-lactam antibiotics and second- and third-generation cephalosporins, the majority (97.6%) of patients had a good outcome. Six patients died, with only one death attributed to *S. pneumoniae* infection. Of these, five received vancomycin and a cephalosporin, and only one had a penicillin-resistant isolate (MIC = 2.0 μg/mL). The authors concluded that standard β-lactam therapy remains effective for pneumonias. A similar study involving 922 cases of pneumococcal bacteremia, 56 of which were nonsusceptible, came to identical conclusions. For non-meningitic disease, reduced antibiotic susceptibility did not alter clinical presentation and had little impact on clinical outcome (Silverman et al., 1999). β-lactam antibiotic therapy was associated with good outcome, and there was no need for vancomycin therapy. In a third study in Pakistan, 595 children with pneumonia diagnosed using the WHO criteria (WHO, 1984) were randomized in a 2:1 ratio to receive cotrimoxazole or amoxicillin (Straus et al., 1998). Children with a cough or difficulty breathing and lower chest indrawing were considered to have severe pneumonia. There were more therapy failures in the cotrimoxazole group than in the amoxicillin group (23% vs. 15%, P = 0.03), with most of the difference accounted for by infants with severe pneumonia (33% vs. 18%, P= 0.01). However, the groups were unbalanced with respect to isolation of resistant *S. pneumoniae* from blood, with more of these patients receiving cotrimoxazole. None of the patients treated with amoxicillin had a clinical isolate of resistant *S. pneumoniae,* but the three that had intermediate susceptibility responded to therapy. In contrast, 4/15 (27%) patients in the cotrimoxazole group with resistant *S. pneumoniae* failed therapy and two of eight with intermediate susceptibility failed therapy. In spite of the imbalance, the use of cotrimoxazole was an independent risk factor for therapy failure. Thus, β-lactam agents should be included in the empiric

management of infections in this age group, but ongoing monitoring for susceptibility patterns is warranted. The addition of macrolides in this age group, particularly in outpatients, is suggested for coverage of *M. pneumoniae* and *C. pneumoniae*. Two multicenter randomized clinical trials comparing erythromycin with either clarithromycin (Block et al., 1995) or azithromycin (Harris et al., 1998) found the newer agents to be equally efficacious, but with much fewer side effects. In the control group in the latter study, those less than 5 years of age received amoxicillin–clavulanate and those between 5 and 16 years of age received erythromycin (Harris et al., 1998). A randomized study with a similar study design of 168 children with community-acquired pneumonia also did not find any differences between amoxicillin–clavulanate recipients and macrolide recipients (Wubbel et al., 1999). The authors of that study concluded that antibiotic choice should be based on clinical judgment. However, this study had limited power to detect differences because of its small overall sample size. Interestingly, this study also detected relatively fewer cases of *C. pneumoniae* and *M. pneumoniae* than did the multicenter randomized trials.

Conclusions and Research Priorities

One of the major dilemmas in the management of pneumonias is the inability to diagnose an etiologic agent. In the past, the conservative route of management was to initiate antibiotics in all who had radiographically confirmed pneumonia. This still appears to be the most prudent course, at this time, given the high frequency of double infections, in which bacterial and viral agents may both be diagnosed in a patient (Heiskanen-Kosma et al., 1998). However, more controlled studies are needed to understand the significance of serodiagnostic methods. Whether some of the pneumococcal seropositive cases, for example, are false positives needs to be determined.

Few clinical trials have been conducted to determine the efficacy of macrolides compared with penicillins. Macrolides have been included as first-line agents in most treatment guidelines on the basis of their coverage of atypical organisms (Bartlett et al., 1998). Given the high success rate of current treatment of pneumonia and the increasing resistance rates to macrolides among group A streptococci (Seppala et al., 1997) and *S. pneumoniae* (Kellner et al., 1996) due to overuse of these agents, however, randomized trials that show an incremental benefit of these agents are needed to justify their inclusion in empiric therapy.

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