

Diagnosis and management of pneumonia in children

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Background. This paper describes challenges in etiologic diagnosis and treatment of childhood community-acquired pneumonia and the means of addressing some of them.

Microbiologic diagnosis. From about one-third to two-thirds of cases of pneumonia can be attributed to a specific etiology depending on which culture, antigen detection and specialized serologic techniques, some of which are unavailable to clinicians, are used. Results of studies in which microbiologic causes have been sought confirm the importance of *Streptococcus pneumoniae* as the primary bacterial cause of pneumonia in infants and children. Viral etiologies become less prevalent and mycoplasmal and chlamydial infections become more prevalent with increasing age.

Empiric treatment. Because definitive information about causative pathogens is seldom available, treatment of pneumonia is most often empiric. Antibiotic therapy can be withheld in mildly ill, ambulatory patients in whom viral infection is likely. Most guidelines suggest initial treatment with orally administered amoxicillin or amoxicillin/clavulanate or with intravenous cefuroxime when patients require hospitalization. In May, 2000, the Centers for Disease Control-convened Drug-Resistant *S. pneumoniae* Therapeutic Working Group identified oral beta-lactams including cefuroxime axetil, amoxicillin and amoxicillin/clavulanate as appropriate options for first line therapy of community-acquired pneumonia in ambulatory adults and children.

Conclusions. New diagnostic techniques such as pneumococcal serologies and polymerase chain reaction testing have improved the ability to determine the microbiologic etiology of childhood pneumonia. Because these tests are not

generally available, empiric treatment is necessary. Efforts to identify new intervention strategies, diagnostic tools, therapies and vaccines will be helpful in managing this disease.

INTRODUCTION

Pneumonia-associated mortality has declined over the decades since penicillin was introduced.^{1, 2} Nevertheless, pneumonia, especially when associated with influenza infection, was responsible for more than 86 000 deaths in 1997.³ Pneumonia remains the most common infectious cause of death in the United States⁴ and incurs substantial morbidity-related costs to society and the health care system.⁵

Pneumonia presents the clinician with challenges in etiologic diagnosis and treatment. This paper describes these challenges and the means, as of the year 2000, of addressing some of them.

MICROBIOLOGIC DIAGNOSIS

Of all of the common pediatric infectious diseases of the respiratory tract, pneumonia is the one for which a microbiologic diagnosis is most difficult to determine. It is estimated that only one-third of cases of pneumonia can be attributed to a specific etiology using culture, antigen detection and serologic techniques readily available to clinicians.⁶ Blood cultures, for example, yield evidence of pathogens in only 10 to 15% of infants and children hospitalized with presumed bacterial pneumonia. In a review of European pediatric studies, Ruuskanen and Mertsola⁷ found that, depending on the extent of laboratory testing performed, the microbial cause of pneumonia could be identified in 20 to 60% of cases.

Hospitalized patients. When microbiologic causes of pneumonia have been determined in children, *Streptococcus pneumoniae* has been identified as the most common bacterial pathogen and respiratory syncytial virus as the most common viral pathogen. In a 3-year study conducted in Finland, Juven et al.⁸ used a variety of laboratory methods including serologic tests and polymerase chain reaction to assess the etiology of community-acquired pneumonia in 254 hospitalized children. A potential etiologic microbial agent was identified in 85% of cases (Table 1). The percentages of patients with viral infection, bacterial infection and

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TABLE 1. Etiology of community-acquired pneumonia in hospitalized patients⁸

Age (yr)	N	Viral Etiology	Bacterial Etiology	Mixed Etiology	All*
<2	108	80†	47	34	93
2–5	84	58	56	33	81
>5	62	37	58	19	76
Total	254	62	53	30	85

* Total with etiology detected.

† Results expressed as percentages of patients.

concomitant viral-bacterial infection were 62, 53 and 30%, respectively. The most common potentially causative pathogens were *S. pneumoniae* (37%), respiratory syncytial virus (29%) and rhinovirus (24%). The last agent is not traditionally considered a pathogen of the lower respiratory tract of children, but in some of these cases it could have predisposed the patient to bacterial superinfection.

The incidence of viral infections in the study of Juven et al. decreased with increasing age of the patient, whereas that of bacterial infections remained fairly stable across age. The percentages of patients aged younger than 2 years, 2 to 5 years and older than 5 years with evidence of viral infections were 80, 58 and 37%, respectively (Table 1). The corresponding numbers for evidence of bacterial infections were 47, 56 and 58%. Only 1 of 125 patients from whom a blood culture was obtained had a positive culture for a bacterial pathogen, a finding confirming the limitation of this method for detecting causative pathogens.

Pneumonia in ambulatory children. The finding of Juven et al. that approximately one-third of these hospitalized patients were infected with *S. pneumoniae* is consonant with data from ambulatory children with pneumonia. In studies conducted in Finland⁹ and the United States,¹⁰ 24 to 33% of infants and children up to 4 years of age were infected with *S. pneumoniae*. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were isolated more often in 5- to 9- and 10- to 16-year olds than in younger patients (Table 2). Like the study of Juven et al.,⁸ these two studies demonstrate an age-related decline in the incidence of viral pneumonia (Table 2).

An age-related increase in the incidence of infection with *M. pneumoniae* and *C. pneumoniae* was also found in studies of childhood community-acquired pneumonia in Massachusetts¹¹ ($n = 420$) and Kentucky¹² ($n =$

260). The percentages of children with evidence of *M. pneumoniae* were, for the Massachusetts and Kentucky studies, respectively, 15 and 23% for children younger than 5 years of age and 43 and 28% for children greater than 5 years of age (Table 3). The percentages of children with evidence of *C. pneumoniae* for the respective studies were 9 and 23% for children younger than 5 years of age and 21 and 31% for children older than 5 years of age (Table 3). The results of these United States studies were consistent despite their being conducted in different regions of the country at different times and using different pathogen detection techniques.

Considered together, the results of these studies confirm the importance of *S. pneumoniae* as the primary bacterial cause of pneumonia in infants and children. The data also indicate that viral etiologies become less prevalent and mycoplasmal and chlamydial infections become more prevalent with increasing age, especially in adolescents and young adults. *Staphylococcus aureus*, *Moraxella catarrhalis* and group A and B streptococci were rarely identified as bacterial causes of childhood pneumonia in these studies. Group A streptococcal pneumonia can occur as a complication of varicella.

In determining the possible roles of *M. pneumoniae* and *C. pneumoniae* in the etiology of pneumonia, serologic tests and polymerase chain reaction, the two primary methods for detecting these pathogens in the clinical setting, may produce discordant results. Positive polymerase chain reaction tests often occur in the presence of negative serologic tests. For example Falck et al.¹³ found that among children with respiratory infections and a positive polymerase chain reaction test, only 4 of 14 patients age 6 years or younger and 12 of 21 patients older than 6 years also had serologic evidence of infection. On the other hand, of 19 children

TABLE 2. Etiology of ambulatory community-acquired pneumonia in two studies^{9, 10}

Patient Age (yr)	Country	<i>Streptococcus pneumoniae</i>	<i>Mycoplasma pneumoniae</i>	<i>Chlamydia pneumoniae</i>	Viral
0–4	Finland ⁹	24*	4	1	37
	Texas ¹⁰	33	6	3	28
5–9	Finland	36	30	13	21
	Texas	14	7	9	10
10–16	Finland	31	51	35	4
	Texas	29	14	14	0

* Results expressed as percentages of patients.

TABLE 3. Etiology of ambulatory community-acquired pneumonia in two studies^{11, 12}; role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*

	<i>Chlamydia pneumoniae</i>		<i>Mycoplasma pneumoniae</i>	
	Massachusetts ¹¹	Kentucky ¹²	Massachusetts	Kentucky
<5 yr	9*	23	15	23
>5 yr	21	31	43	28
Total	18.6	29.2	29.5	26.5

* Results expressed as percentages of patients with pneumonia.

with serologic evidence of *C. pneumoniae*, 17 also had positive polymerase chain reaction tests for presence of the pathogen in the nasopharynx.

Even when respiratory pathogens have been identified by polymerase chain reaction in the upper respiratory tract, their causal role in pneumonia can be difficult to assess. The study of Falck et al.¹³ examined the prevalence of *C. pneumoniae* in healthy children with no evidence of respiratory tract infections as well as in the ill children described above. Although positive polymerase chain reaction tests for *C. pneumoniae* were obtained most often in the sick children (38% of patients ages 0 to 5 years and 51% of patients ages 6 to 10 years), positive tests were also obtained in healthy children (11% of children ages 0 to 5 years and 13% of children ages 6 to 10 years). Thus a positive polymerase chain reaction for *C. pneumoniae* in the upper respiratory tract does not necessarily imply that it is the etiologic agent of that patient's lower respiratory disease.

Likewise, the identification of a potentially causative pathogen does not preclude the possibility of an etiologic contribution from other pathogens. Respiratory viral infections frequently are complicated by bacterial superinfections as, for example, when bacterial pneumonia occurs with or follows infection with influenza A or B virus. The high probability of infection with viral and bacterial copathogens in pneumonia is illustrated by the finding of Juven et al.⁸ (described above) of mixed viral-bacterial infection in 30% of the children hospitalized with community-acquired pneumonia. Similarly, Ruuskanen and Mertsola⁷ found evidence for mixed viral-bacterial infection in 16 to 34% of cases in their survey of European studies of childhood community-acquired pneumonia.

DIAGNOSIS

Clinical manifestations. The clinical manifestations of pneumonia are diverse. Community-acquired pneumonia has classically been characterized by sudden onset of fever, tachypnea and cough. These symptoms are frequently preceded by a relatively minor upper respiratory infection characterized by low grade fever and rhinorrhea. It is often difficult to distinguish clinically children with viral pneumonia from those with bacterial disease.

The symptomatology of community-acquired pneumonia in children has not been systematically studied. Many children seek medical attention without specific respiratory symptoms and many may appear only mildly ill.⁷ Tachypnea accompanied by crackles (i.e. rales) on auscultation suggests the diagnosis of pneumonia, although rales are often not heard in children with pneumonia, particularly if the child is dehydrated. Wheezing can be found in children with viral or mycoplasmal pneumonia.⁷

Ruuskanen and Mertsola⁷ note that presence of tachypnea may be the best way to distinguish a lower respiratory tract infection from an upper respiratory tract infection. Guidelines developed by the World Health Organization (WHO) for clinical diagnosis of pneumonia in the developing world have emphasized tachypnea and retractions as the best indicators.¹⁴ The WHO defines tachypnea as >50 breaths/min in infants less than 1 year of age and >40 breaths/min in children 1 year or older. Tachypnea is also a manifestation of asthma or bronchiolitis.

Radiographic findings. Because the clinical manifestations of pneumonia are diverse and are shared by other respiratory infections, they are not informative in arriving at a definitive diagnosis. Therefore chest radiographs are often used to confirm the presence and determine the location of the pulmonary infiltrate. Radiographic features are one of four factors that Nelson¹⁵ considers in assessing a child with community-acquired pneumonia. He and others suggest that pneumococcal infection is characterized radiographically by lobar consolidation and viral infection by interstitial or bilateral bronchoalveolar or peribronchial infiltrates.

Epidemiologic factors. In addition to radiographic features, Nelson considers epidemiologic factors in narrowing the possibilities among possible etiologic agents. Respiratory syncytial and influenza virus infections typically peak in the late fall and winter months in the United States, whereas bacterial pneumonia exhibits less marked seasonal fluctuations. Because the chances of infection with different pathogens, including viruses, vary with age, age should be considered in determining the most likely pathogens. Finally, Nelson emphasizes the importance of considering the child's immunization status. If a child has received influenza vaccination during the same season that he or she experiences possible symptoms of pneumonia, influenza viruses A and B are less likely to be the causative pathogens. Likewise, complete immunization with the *Haemophilus* vaccine eliminates the possibility of *Haemophilus influenzae* type b as the pathogen of pneumonia.

Laboratory tests. Noninvasive diagnostic tests are typically used in attempts to determine the microbio-

logic cause of pneumonia; invasive procedures are reserved for hospitalized patients with underlying disease who fail to respond to initial antibiotic therapy. Sputum samples are never used to identify organisms responsible for bacterial pneumonia in infants and children. Cultures of these specimens and of the nasopharynx do not correlate with those of the lower respiratory tract and should not be performed as a means to ascertain etiology. Children do not produce sufficient sputum for collection. On the other hand, nasopharyngeal mucus is used for antigen detection and culture to identify viral pathogens of the respiratory tract. The presence of a virus in the upper respiratory tract does not necessarily imply that it is the cause of pneumonia. The viral illness could have predisposed to bacterial superinfection in the lower respiratory tract.

For very ill patients and those with underlying disease, bronchoscopy is used for direct viewing of the lower respiratory tract and for collection of material (bronchoalveolar lavage) for specific staining procedures and cultures. Transtracheal aspiration and percutaneous transthoracic lung puncture are rarely performed in children.

Thoracentesis can be used to determine the existence of effusion or empyema. If empyema is present the bacterial etiology should be established, and immediate drainage, which decreases the length and severity of illness, is indicated. In cases of effusion only, drainage is usually unnecessary unless loculations occur and symptoms persist, as can be seen in some patients with pneumococcal disease.

An important new tool in managing empyema, video-assisted thorascopy can improve clinical outcomes and quicken recovery. In a 1992 to 1998 study¹⁶ of children 3 months to 15 years of age with empyema, the use of video-assisted thorascopy, as compared with chest tube drainage, was associated with significantly lower numbers of preoperative days (1 vs. 5.5) and postoperative recovery days (6 vs. 9) as well as fewer total days of hospitalization (7 vs. 12) and fewer thoracotomies (0 vs. 9) (Table 4). The most common etiology of empyema in this study was *S. pneumoniae* (32% of patients) fol-

lowed by *Staphylococcus aureus* (8% of patients) and *H. influenzae* (1% of patients).

EMPIRIC TREATMENT

To prescribe or withhold antibiotic therapy.

Because definitive information about causative pathogens is seldom available, treatment of pneumonia is most often empiric. Clinicians first need to decide whether or not to withhold antibiotic treatment. Although some suggest that antibiotic therapy is always indicated in pneumonia because of the difficulty in excluding the possibility of bacterial infection,⁷ others, including the author of this review, believe that antibiotic therapy can be withheld in mildly ill, ambulatory patients in whom viral infection is likely.¹⁴

Recommendations for antibiotic treatment of bacterial pneumonia differ among experts. However, most guidelines (reviewed by Ruuskanen and Mertsola⁷) suggest initial treatment with orally administered amoxicillin or penicillin or with intravenous cefuroxime when patients require hospitalization. For ambulatory pneumonia, amoxicillin is usually administered if there is high likelihood of infection with penicillin-susceptible pneumococci. If penicillin resistance is prevalent in a community or if infection with *M. pneumoniae* or *C. pneumoniae* is likely, intravenous treatment with a beta-lactam drug, a macrolide or both drugs is usually indicated. An exception would be the child with nonsevere illness in whom high dosage (80 to 100 mg/kg/day) amoxicillin would be appropriate.

Three studies¹⁰⁻¹² published in the past 6 years compared the efficacy of conventional therapy with drugs such as amoxicillin or amoxicillin/clavulanate with that of newer macrolides such as azithromycin and clarithromycin. The results show similar effectiveness among therapies, all of which produced excellent clinical cure rates. For example Wubbel et al.¹⁰ found that 143 of 147 patients treated with azithromycin, erythromycin estolate or amoxicillin/clavulanate were classified as being clinically cured. Response rates did not differ as a function of the drug that was used, regardless of whether analyses included all treated patients or only patients with a presumed bacterial etiology of pneumonia. It is likely that many of these children had viral illnesses that did not require antibiotic treatment.

Empiric treatment for penicillin-resistant pneumococcus. The continued proliferation of penicillin-resistant pneumococcus has provoked concern about the efficacy of penicillin and other beta-lactams for the treatment of pneumonia. Two studies examined the efficacy of beta-lactams in penicillin-susceptible compared with penicillin-resistant pneumococcal disease. In the first study¹⁷ 32% of the 108 children enrolled had penicillin-resistant infections including pneumonia. Clinical improvement rates 48 h after

TABLE 4. Video-assisted thorascopy in children with empyema¹⁶

	Chest Tube (n = 60)	Chest Tube/Video- assisted Thorascopy (n = 38)	Video-assisted Thorascopy (n = 41)
No. of procedures	2*	2†	1†
Days with chest tube	5	3†	3†
Preoperative days	5.5	4.5	1†
Postoperative days	9	5†	6†
Days of hospitalization	12	11	7†
No. of thoracotomies	9	3†	0†

* Median value.

† $P < .05$ vs. chest tube.

initiation of beta-lactam therapy administered parenterally did not differ between penicillin-susceptible pneumococcal infections and penicillin-resistant infections in the study sample considered as a whole (64% of penicillin-susceptible infections and 60% of penicillin-resistant infections with improvement) or in the 78 children with pneumonia (93% of penicillin-susceptible infections and 88% of penicillin-resistant infections with improvement). In the second study¹⁸ 97.6% of 254 children with pneumococcal pneumonia had a good response to therapy (a second or third generation cephalosporin administered parenterally followed by a course of oral antibiotics) and efficacy did not differ between patients with disease caused by penicillin-susceptible pneumococci and those with disease caused by penicillin-resistant pneumococci. Available evidence indicates that standard intravenous therapy with a penicillin or cephalosporin remains effective against penicillin-resistant pneumococcus.

In May 2000 the Drug-Resistant *S. pneumoniae* Therapeutic Working Group, a team of clinicians, academicians and public health experts convened by the CDC, published guidelines on management of community-acquired pneumonia in this era of increasing pneumococcal resistance.¹⁹ They identified oral beta-lactams including cefuroxime axetil, amoxicillin and amoxicillin/clavulanate as appropriate options for first line therapy of ambulatory community-acquired pneumonia. Although macrolides were also considered appropriate for adults, they were generally not considered the best choice for children younger than 5 years because their broad spectrum of activity against atypical pathogens was not deemed important for this young age group. Doxycycline, which also has broad spectrum coverage against atypical pathogens and was considered appropriate first line therapy for adults, is not approved by the US Food and Drug Administration for use by children younger than 8 years of age.

Pneumococcal conjugate vaccine. The pneumococcal conjugate vaccine will likely be effective in reducing pneumococcal lower respiratory infections, especially those caused by antibiotic-resistant strains. The pneumococcal conjugate vaccine administered at 2, 4 and 6 months of age followed by a booster at 12 months was recently shown²⁰ to reduce by 33% the incidence of pneumonia accompanied by any abnormal radiograph and to reduce by 73% pneumonia associated with a ≥ 2.5 cm consolidation on chest radiograph, a presentation highly suggestive of lobar pneumonia of pneumococcal etiology.

CONCLUSIONS

The advent of new diagnostic techniques such as pneumococcal serology and polymerase chain reaction

testing has significantly improved the ability to determine the microbiologic etiology of childhood pneumonia. Because these tests are not generally available, empiric treatment is necessary. Efforts to identify new intervention strategies, diagnostic tools, therapies and vaccines will be helpful in managing this disease.

REFERENCES

1. Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. *JAMA* 1999;281:61–6.
2. Dowell SF, Kupronis BA, Zell ER, et al. Mortality from pneumonia in children in the United States, 1939 through 1996. *N Engl J Med* 2000;342:1399–407.
3. Deaths: Final data for 1997. National Center For Health Statistics. *Vital Health Stat Series No. 47(19)*, 1999.
4. Mossad SB. Underused options for preventing and treating influenza. *Cleveland Clin J Med* 1999;66:19–23.
5. Winter JG. The scope of lower respiratory tract infection. *Infection* 1991;19(Suppl 7):S359–64.
6. McCracken GH. Etiology and treatment of pneumonia. *Pediatr Infect Dis J* 2000;19:273–7.
7. Ruuskanen O, Mertsola J. Childhood community-acquired pneumonia. *Semin Respir Infect* 1999;14:163–72.
8. Juven T, Mertsola J, Waris M, et al. Etiology of community-acquired pneumonia in 254 hospitalized children. *Pediatr Infect Dis J* 2000;19:293–8.
9. Heiskanen-Kosma T, Korppi M, Jokinen C, et al. Etiology of childhood pneumonia: serologic results of a prospective, population-based study. *Pediatr Infect Dis J* 1998;17:986–91.
10. Wubbel L, Muniz L, Ahmed A, et al. Etiology and treatment of community-acquired pneumonia in ambulatory children. *Pediatr Infect Dis J* 1998;18:98–104.
11. Harris JS, Kolokathis A, Campbell M, et al. Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children. *Pediatr Infect Dis J* 1998;17:865–71.
12. Block S, Hedrick J, Hammerschlag M, et al. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in pediatric community-acquired pneumonia: comparative efficacy and safety of clarithromycin vs. erythromycin ethylsuccinate. *Pediatr Infect Dis J* 1995;14:471–7.
13. Falck G, Gnarp J, Gnarp H. Prevalence of *Chlamydia pneumoniae* in healthy children and in children with respiratory tract infections. *Pediatr Infect Dis J* 1997;16:549–54.
14. The WHO Young Infants Study Group. Serious infections in young infants in developing countries: rationale for a multicenter study. *Pediatr Infect Dis J* 1999;18(10 Suppl):S4–7.
15. Nelson JD. Community-acquired pneumonia in children: guidelines for treatment. *Pediatr Infect Dis J* 2000;19:251–3.
16. Doski JJ, Lou D, Hicks BA, et al. Management of parapneumonic collections in infants and children. *J Pediatr Surg* 2000;25:265–8.
17. Friedland IR. Comparison of the response to antimicrobial therapy of penicillin-resistant and penicillin-susceptible pneumococcal disease. *Pediatr Infect Dis J* 1995;14:885–90.
18. Tan TQ, Mason EO Jr., Barson WJ, et al. Clinical characteristics and outcome of children with pneumonia attributable to penicillin-susceptible and penicillin-nonsusceptible *Streptococcus pneumoniae*. *Pediatrics* 1998;102:1369–75.
19. Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance. *Arch Intern Med* 2000;160:1399–408.
20. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. *Pediatr Infect Dis J* 2000;19:187–95.