Pneumonia in pediatric outpatients: Cause and clinical manifestations

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**The cause and clinical manifestations of pneumonia were studied in 98
pediatric outpatients. A viral diagnosis was established in 38 (39%) of the 98
patients, and a bacterial diagnosis in 19 (19%). Ten (53%) of the 19 patients with
bacterial pneumonia had a concurrent viral infection. No clinical, laboratory,
or radiographic findings that would reliably differentiate viral from bacterial
infection were identified. This study suggests that bacterial pneumonia is more
common in pediatric outpatients than previously reported, and that the
clinical, laboratory, and radiographic findings in patients with bacterial infec-
tion may be indistinguishable from findings in patients with viral infection.
(J PEDIATR 1987;111:194-200)**

Most children with pneumonia are managed as outpa-
tients.[1] In contrast, most published information about
pneumonia, particularly bacterial pneumonia, has been
derived from hospitalized patients. This situation reflects
the lack of simple, reliable methods for establishing a
diagnosis of bacterial infection in the outpatient setting.
The diagnosis of bacterial pneumonia in pediatric patients
generally depends on isolation of the infecting organism
from the blood. Blood cultures, however, have been
reported to be positive in only 13% of patients with
bacterial pneumonia documented by lung punctures.[2] Lung
puncture, which provides sensitive and specific detection of
bacterial pneumonia, is too invasive to be used in patients
who are not severely ill.

The detection of bacterial antigen in body fluids by
counterimmunoelectrophoresis has proved useful for bac-
terial diagnosis in a number of clinical syndromes.[3] Anti-
gen can be detected by CIE in the sputum, serum, and
urine of patients with bacterial pneumonia.[3-10] Antigen
detection methods appear to be more sensitive than blood
cultures for the diagnosis of bacterial pneumonia, although
the absolute sensitivity of these methods is not known.

The purpose of this study was to define the cause and
clinical manifestations of radiographically proved pneumo-
nia in a pediatric outpatient population by using antigen
detection for the diagnosis of bacterial infection, and virus
isolation, antigen detection, and serologic studies for the
diagnosis of viral infection.

CIE	Counterimmunoelectrophoresis
CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assay
HIB	*Hemophilus influenzae* type b
MDCK	Madin-Darby canine kidney cells
PMN	Polymorphonuclear leukocyte
RSV	Respiratory syncytial virus

METHODS

Patients seen in the outpatient clinic or emergency room
of the Children's Hospital of Northern California were
eligible for admission to the study if they (1) were 2
months to 15 years of age, (2) had an infiltrate on chest
radiograph, and (3) had a temperature ≥38° C or a
history of fever. Patients with underlying pulmonary or
immunologic disease were excluded. Patients were enrolled

in the study from December 1982 to March 1984. No attempt was made to enroll all patients who were eligible for the study. Enrollment was dependent primarily on the involvement of the investigators in the care of the patient; the majority of patients were enrolled by one investigator (A.E.L.). One hundred nineteen patients were initially enrolled; 21 patients were subsequently excluded from the data analysis because urine specimens or viral cultures were not obtained.

Specimens collected. After informed consent was obtained, a history and physical examination was done to address specific clinical findings. A throat swab and a nasopharyngeal swab were placed into viral collecting broth (Earle balanced salt solution with 0.5% bovine serum albumin) and frozen at $-70°$ C. A urine specimen obtained either as a voluntarily voided specimen or in a urine collection bag was refrigerated until transported to the laboratory. Acute serum specimens were collected at the time of the initial visit, and convalescent sera 2 to 3 weeks later. Serum specimens were frozen at $-20°$ C until assayed for antibody. Viral cultures, urine, and sera were transported to the University of Utah for analysis. Blood cultures were not done routinely for the study, but blood cultures done as part of the medical management of the patient were included in the data analysis.

Viral cultures. The specimens received in the laboratory for viral culture were treated with penicillin (500 U/mL) and streptomycin (250 µg/mL) before inoculation into duplicate tube cultures of human foreskin fibroblasts, Hep-2, and primary cynomolgus monkey kidney cells. Madin-Darby canine kidney cells were also inoculated during the seasons when influenza virus was prevalent in the study area. One set of cultures from each specimen was incubated at $36°$ C in a stationary rack, and the other set was incubated in a roller drum at $33°$ C. Cell culture fluids from the monkey kidney and MDCK cultures were tested for the presence of hemagglutinating viruses on days 5 and 20 after inoculation.

RSV antigen detection. An aliquot of each viral culture specimen was tested for respiratory syncytial virus antigen using a commercially available ELISA assay (Abbott RSV-EIA, Abbott Laboratories, (North Chicago, Ill.). Ten nasal wash specimens collected from volunteers infected with rhinovirus type 39 were used as controls, and were negative by this assay.

Serology. Acute and convalescent sera were tested for antibody to RSV, adenovirus, influenza A and B, parainfluenza types 1 to 3, and *Mycoplasma pneumoniae* by complement fixation. Serologic testing for coronavirus 229E was done by a microtiter neutralization assay.[11] A fourfold increase in antibody from the acute to the convalescent serum was considered evidence of infection.

Counterimmunoelectrophoresis. Urine specimens were tested for the presence of bacterial capsular polysaccharide using pneumococcal omniserum (Statens Seruminstitute, Copenhagen) and burro antiserum to *Haemophilis influenzae* type b (provided by Dr. John Robbins, Bethesda, Md.). Each specimen was concentrated 20- to 100-fold (depending on the volume of urine collected) by ethanol precipitation.[12] CIE was done in a continuous system with 3×1 inch glass slides coated with 3 mL 1% agarose (electrophoresis grade, Sigma Diagnostics, St. Louis) in veronal buffer, pH 8.8. Wells 3 mm in diameter and 3 mm apart were filled with the appropriate sample, and the electrophoresis was run at a constant current of 6 mA per slide for 1 hour. The slides were examined for precipitin lines immediately and after immersion in saline solution overnight at $4°$ C. To determine the reproducibility of the assay, pneumococcal polysaccharide in broth medium was serially diluted in control urine. An aliquot of the highest dilution at which antigen could be detected by CIE was further diluted 1:100 and then reconcentrated by ethanol precipitation. Refrigerated and frozen aliquots of the original limiting dilution and the reconcentrated specimen were then run with different lots of agarose slides. Freezing or ethanol precipitation appeared to have no effect on the reproducibility of the method, but there was variation in the sensitivity of different lots of agarose slides. For this reason, urine specimens with sufficient volume for repeat concentration were tested twice for the presence of bacterial antigen. Ten (14%) of the 74 specimens retested had discordant results on the repeat CIE assay, including four that were positive only on the repeat assay. Because all control specimens were negative regardless of the lot of slides used, specimens in which bacterial antigen was detected by either of the two assays were considered positive.

Fifty-one urine specimens, 19 from patients with otitis media but no other focus of infection and 32 from children with no evidence of infection, were concentrated and run as negative controls. These specimens were collected throughout the course of the study and were tested with different lots of CIE slides by a technologist who was not aware of which specimens were from patients and which were from controls. No negative control specimen had detectable bacterial antigen in this assay.

C-reactive protein assay. Ninety-five of the 98 patients enrolled in the study had acute serum available for determination of CRP concentration. CRP assays were done by rate nephelometry (Beckman Immunochemistry Systems, Beckman Instruments Inc., Fullerton, Calif.). Values > 1.5 mg/dL were considered positive.

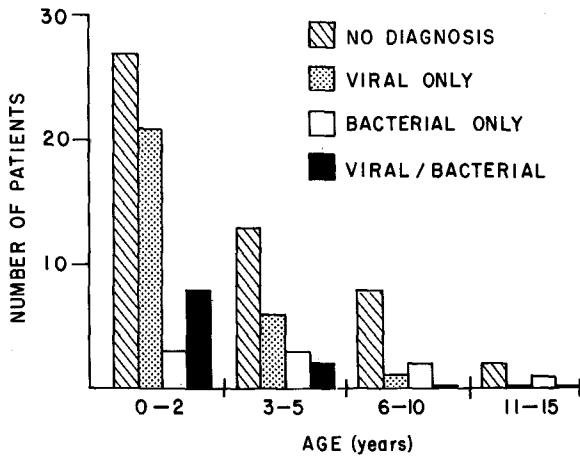**Statistical testing.** Proportions were compared by the Fisher exact test. Continuous variables in groups of

Fig. 1. Etiologic diagnoses by age in 98 pediatric outpatients with pneumonia.

Table. Etiologic diagnoses in 98 pediatric outpatients with pneumonia

	n	%
Viral infection	38	39
Respiratory syncytial virus	27	28
Parainfluenza	5	5
Rhinovirus	2	2
Influenza	2	2
Enterovirus	2	2
Adenovirus	1	1
Coronavirus 229E	1	1
Bacterial infection	19	19
Pneumococcus	17	17
Haemophilus influenzae	2	2
No etiologic diagnosis	51	52

patients were compared by a two-sided Mann-Whitney U test.

RESULTS

Ninety-eight patients with radiographically documented pneumonia were included in the data analysis. The male/female ratio was 1.3:1, and 59 (61%) of the patients enrolled were younger than 2 years of age (Fig. 1). Although patients were enrolled in the study in all months of the year, the majority were enrolled in the winter and early spring. In addition to the urine and viral culture specimens collected for all patients, 75 (77%) patients had a blood culture done and 50 (51%) had paired sera available for analysis.

Etiologic diagnoses. Thirty-eight (39%) of the 98 patients had a documented viral infection (Table). Twenty-five (66%) of the 38 infections were diagnosed by virus isolation or antigen detection only, five (13%) by serologic study only, and eight (21%) by both serologic study and virus isolation or antigen detection. Twenty-seven (71%) of the 38 patients with viral infection were infected with RSV. Two patients with RSV infection had a concurrent infection with another virus, one with influenza B and one with coronavirus 229E.

Bacterial infection was detected in 19 (19%) of the 98 patients (Table). Seventeen patients had a pneumococcal infection, and two were infected with HIB. The diagnosis of bacterial infection was made by detection of bacterial antigenuria in 17 patients. Three patients had pneumococcal bacteremia, including two patients who did not have detectable antigenuria. No etiologic diagnosis was established in 51 (52%) of the 98 patients.

Ten (53%) of the 19 patients with bacterial pneumonia

had a concurrent viral infection. The viral infections in these patients included RSV (four patients), parainfluenza type 3 (three patients), and echovirus type 6, rhinovirus, and adenovirus (one patient each). Parainfluenza virus was isolated from three (16%) of 19 patients with a concurrent bacterial infection and from two (3%) of 79 patients without a bacterial diagnosis (P = 0.05). In contrast, RSV was isolated from four (21%) of the 19 patients with bacterial infection and from 23 (29%) of the 79 patients with no bacterial diagnosis.

Clinical and laboratory findings. The patients with a viral infection only were compared with those patients with a bacterial infection either alone or combined with viral infection, to determine whether clinical, laboratory, or x-ray finding would reliably detect patients with bacterial infection.

The patients with viral pneumonia had a mean age of 2.1 years compared with 3.1 years in patients with bacterial pneumonia. The mean duration of illness before seeking medical care was 3.8 days in both the viral and bacterial infection groups. No difference was found in the proportion of patients in each group who reported ill family members, rhinorrhea, cough, myalgia, headache, respiratory distress, anorexia, abdominal pain, or vomiting. Similarly, there were no significant differences in the proportion of patients in each group who had high fever (temperature $\geq 40°$ C), decreased air exchange, rales, or associated otitis media on physical examination. The only difference noted between the two groups was the incidence of wheezing, which was present either by history or on physical examination in 12 (43%) of the 28 patients with viral infection alone, compared with three (16%) of the 19 patients with bacterial infection (P = 0.05). Two of the three patients with bacterial pneumonia associated with wheezing had a concurrent viral infection. Thus no histor-
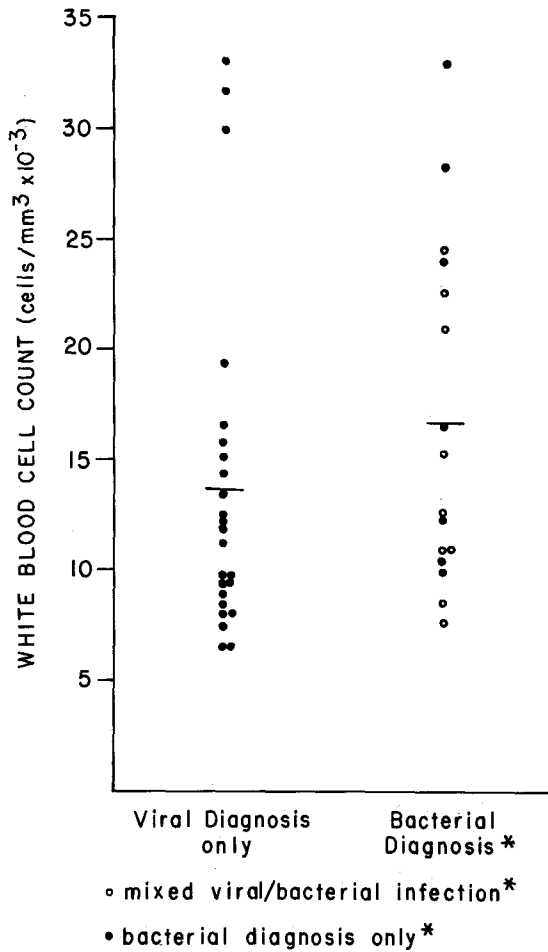
Fig. 2. White blood cell counts in patients with viral pneumonia alone and patients with bacterial pneumonia either alone or associated with viral infection.
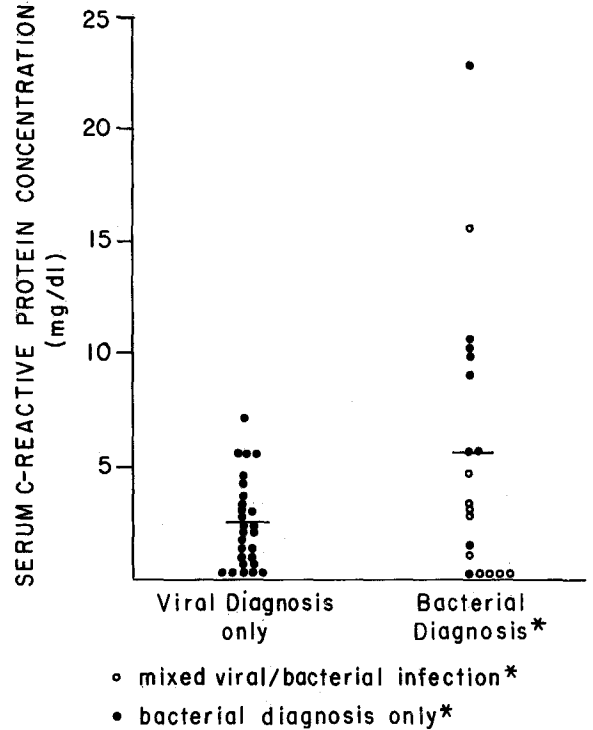

Fig. 3. Serum C-reactive protein in patients with viral pneumonia alone and patients with bacterial pneumonia either alone or associated with viral infection.

ical and clinical findings that would consistently differentiate viral from bacterial infection were identified. No significant differences in clinical findings were noted between the patients in whom no etiologic diagnosis was made and the patients with viral or bacterial infection.

Laboratory findings. White blood cell counts were done in 77 (79%) and differential counts in 76 (78%) of the 98 patients enrolled in the study. Patients with viral infection had a mean ± SD WBC count of 13.7 ± 7.7 cells/mm³ (Fig. 2) with 47% polymorphonuclear leukocytes and 11% bands, compared with patients with bacterial infection, who had a mean WBC count of 16.9 ± 7.8 cells/mm³ (Fig. 2) with 58% PMNs and 12% bands. The mean WBC count was not different in the two groups, but the percentage of total neutrophils was significantly greater in the patients with bacterial infection (P = 0.03). The proportion of patients with an increased WBC (>15,000 mm³), or

increased percentage of total neutrophils (>75%) or bands (>15%) was not different in the two groups.

Serum was available for determination of CRP concentration for 97 (99%) of the patients. The mean ± SD CRP concentration in the patients with viral infection was 2.5 ± 1.9 mg/dL, compared with 5.7 ± 6.1 mg/dL in patients with bacterial infection (Fig. 3). Fifteen (56%) of 27 patients with viral infection had a positive CRP (>1.5 mg/dL), compared with 12 (63%) of 19 patients with bacterial infection. The differences in the mean CRP concentration and in the proportion of patients with a positive CRP were not statistically significant.

Radiographic findings. Chest radiographs for 37 (79%) of the 47 patients in whom an etiologic diagnosis was made were available for review by one of us (R.B.T.). The distribution and pattern of the infiltrates were evaluated without knowledge of the patients' etiologic diagnoses. Bilateral infiltrates were noted in three (23%) of the x-ray studies from 13 patients with bacterial pneumonia and in nine (38%) of the x-ray studies from 24 patients with viral pneumonia. The infiltrate was alveolar in five (38%) of the patients with bacterial pneumonia, compared with 16 (67%) of the patients with viral infection alone. The remaining patients had interstitial infiltrates without asso-

ciated alveolar involvement. None of the 98 patients in the study had radiographic evidence of pleural effusion.

Twenty (21%) of the patients enrolled in the study were subsequently hospitalized for treatment of pneumonia. Patients younger than 3 years of age were more likely to be admitted (17 of 59, 29%) than were older patients (three of 38, 8%), regardless of etiologic diagnosis (P <0.01). Of the patients younger than 3 years of age, six (55%) of 11 with bacterial or combined infection were hospitalized, compared with four (19%) of 21 with viral infection alone (P = 0.05).

DISCUSSION

The results of this study indicate that bacterial infection is a more common cause of pneumonia in pediatric outpatients than previous studies would suggest. Furthermore, patients with bacterial infection cannot be reliably differentiated from patients with nonbacterial pneumonia by clinical, laboratory, or x-ray findings.

In previous studies of pneumonia in pediatric outpatients, viral or *Mycoplasma* infection has been detected in 17% to 31% of those studied.[1, 13-15] The combination of virus isolation and antigen detection with serology in a high proportion of patients resulted in a viral diagnosis in 39% of the patients in our study. The absence of *M. pneumoniae* infection is unexplained, but may be related to the fact that only 14 patients older than 5 years of age were enrolled in the study.

The study of bacterial pneumonia in pediatric patients is difficult because of the lack of a simple yet sensitive test for bacterial infection. In previous studies of hospitalized patients, blood culture had a sensitivity of only 13% compared with lung puncture[2] and 15% compared with antigen detection.[16] McCarthy et al.,[17] in a study of pneumonia in outpatients, detected bacterial infection in five (3%) of 156 patients on the basis of a positive blood culture. In our study, three (3%) of the 98 patients had a positive blood culture, compared with 17 (17%) of 98 who had antigenuria. This information suggests that the true incidence of bacterial pneumonia in pediatric outpatients is higher than the incidence reported in studies in which the diagnosis is based on blood cultures. The incidence of bacterial infection in this study must be interpreted with caution, however. Patients were not enrolled until a chest radiograph had been found to be positive. Furthermore, no attempt was made to enroll all patients who were eligible for the study. These factors could have introduced a bias toward enrolling the patients who were more ill. The fact that the hospitalization rate (21%) was similar to the rate (15%) reported in a previous field study of respiratory disease in pediatric patients[1] suggests that this bias did not have a major effect. The possibility that bacterial infec-

tions were present but not detected by CIE must also be considered when evaluating these data. Infections caused by organisms other than *Streptococcus pneumoniae* and HIB were not sought. Furthermore, the sensitivity of the CIE assay is unknown, and it is probable that some patients with pneumococcal or HIB pneumonia were not detected by CIE of concentrated urine or by blood culture.

The assumption that the presence of bacterial antigenuria in a patient with pneumonia indicates a bacterial cause of the pneumonia is critical to the conclusions of this study. A previous study[2] has compared the detection of antigen in serum with the results of lung puncture aspirates, and concluded that the presence of pneumococcal antigen in the serum of patients with pneumonia indicates the presence of pneumococcal pneumonia. The specificity of the antigen detection assay used in this study was documented by the absence of antigenuria in 32 healthy children and 19 patients with otitis media. The detection of antigen in urine by CIE has also been found to be specific when used for the diagnosis of bacterial pneumonia in adults;[4, 7] pneumococcal antigen was not detected in the urine of healthy controls or patients infected with other pathogens. The absence of bacterial antigenuria in control subjects suggests that simple colonization of the upper respiratory tract does not produce detectable antigen in the urine. A recent study has reported the use of latex particle agglutination and staphylococcal coagglutination for detection of bacterial antigens in pediatric outpatients with lower respiratory tract infection.[18] Although only 7% of the patients in the study had radiographic evidence of pneumonia, 24% had bacterial antigenuria. Antigen was also detected in 16% of patients with otitis media and in 4% of healthy controls, however, suggesting that these methods may be less useful than CIE in the setting of lower respiratory tract disease.

The observation that 53% of the patients with bacterial pneumonia had a concurrent viral infection confirms observations made previously in hospitalized patients. Five studies in which the diagnosis of bacterial infection was established by reliable methods reported concurrent viral infection in 25% to 75% of patients with bacterial pneumonia.[16, 19-22] The finding that concurrent infection occurs with equal frequency in both inpatients and outpatients indicates that concurrent viral and bacterial infection is not associated with unusually severe disease, a suggestion that is further supported by the clinical findings in our study. The high proportion of patients with bacterial pneumonia who have concurrent viral and bacterial infection is consistent with the speculation that viral infections may be important in the pathogenesis of bacterial pneumonia.

No specific clinical or laboratory findings were identi-

fied in this study that would reliably differentiate patients with bacterial infection from patients with nonbacterial pneumonia. McCarthy et al.[17] have reported that positive CRP was significantly associated with bacteremia in patients with pneumonia. Although different methods were used for the CRP determination in the two studies, the most likely explanation for the different finding is that most of the patients with bacterial pneumonia in our study did not have detectable bacteremia and were relatively mildly ill. The observation that viral and bacterial pneumonia could not be differentiated by radiographic findings is consistent with previous reports.[23, 24] That many of the patients with viral infection had clinical, laboratory, and radiographic findings usually considered characteristic of bacterial pneumonia may simply reflect insensitivity in the detection of bacterial infection. Of greater interest was the finding that many of the patients with documented bacterial infection did not have these characteristics. It is possible that statistically significant differences would have been found between patients with viral and bacterial pneumonia if larger numbers of patients had been evaluated. The broad spectrum of illness in the patients with bacterial infection suggests, however, that the accurate detection of bacterial pneumonia in individual patients will be difficult. This information indicates that decisions about the use of antibiotics in patients with pneumonia cannot be based on the results of specific clinical, laboratory, or x-ray findings but should depend on the overall assessment of the patient.[25, 26]

These data demonstrate that detection of bacterial antigen in the urine of patients with pneumonia is a useful tool for the study of the epidemiology and clinical manifestations of this disease. Antigen detection has limited usefulness in the management of pediatric outpatients with uncomplicated pneumonia, because the majority of these patients respond to inexpensive and nontoxic antibiotic therapy and a precise etiologic diagnosis is not necessary for appropriate care.

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