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Epidemiology and Clinical Characteristics of Community-Acquired Pneumonia in Hospitalized Children

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ABSTRACT. *Objectives.* **The precise epidemiology of childhood pneumonia remains poorly defined. Accurate and prompt etiologic diagnosis is limited by inadequate clinical, radiologic, and laboratory diagnostic methods. The objective of this study was to determine as precisely as possible the epidemiology and morbidity of community-acquired pneumonia in hospitalized children.**

Methods. **Consecutive immunocompetent children hospitalized with radiographically confirmed lower respiratory infections (LRIs) were evaluated prospectively from January 1999 through March 2000. Positive blood or pleural fluid cultures or pneumolysin-based polymerase chain reaction assays, viral direct fluorescent antibody tests, or viral, mycoplasmal, or chlamydial serologic tests were considered indicative of infection by those organisms. Methods for diagnosis of pneumococcal pneumonia among study subjects were published by us previously. Selected clinical characteristics, indices of inflammation (white blood cell and differential counts and procalcitonin values), and clinical outcome measures (time to defervescence and duration of oxygen supplementation and hospitalization) were compared among groups of children.**

Results. **One hundred fifty-four hospitalized children with LRIs were enrolled. Median age was 33 months (range: 2 months to 17 years). A pathogen was identified in 79% of children. Typical respiratory bacteria were identified in 60% (of which 73% were *Streptococcus pneumoniae*), viruses in 45%, *Mycoplasma pneumoniae* in 14%, *Chlamydia pneumoniae* in 9%, and mixed bacterial/viral infections in 23%. Preschool-aged children had as many episodes of atypical bacterial LRIs as older children. Children with typical bacterial or mixed bacterial/viral infections had the greatest inflammation and disease severity. Multivariate logistic-regression analyses revealed that high temperature (≥38.4°C) within 72 hours after admission (odds ratio: 2.2; 95% confidence interval: 1.4–3.5) and the presence of pleural effusion (odds ratio: 6.6; 95% confidence interval: 2.1–21.2) were significantly associated with bacterial pneumonia.**

Conclusions. **This study used an expanded diagnostic armamentarium to define the broad spectrum of pathogens that cause pneumonia in hospitalized children. The data confirm the importance of *S pneumoniae* and the frequent occurrence of bacterial and viral coinfections in children with pneumonia. These findings will facilitate age-appropriate antibiotic selection and future evaluation of the clinical effectiveness of the pneumococcal conjugate vaccine as well as other candidate vaccines. *Pediatrics* 2004;113:701–707; *community-acquired pneumonia, child, epidemiology, diagnosis, etiology, hospitalized.***

ABBREVIATIONS. LRI, lower respiratory infection; PCR, polymerase chain reaction; DFA, direct fluorescent antibody; RSV, respiratory syncytial virus; Ig, immunoglobulin; WBC, white blood cell.

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The quest to define accurately and promptly the causative agents of lower respiratory infections (LRIs) in children has been impeded by inadequate clinical, radiologic, and laboratory diagnostic methods. A limited number of well-defined prospective studies that used conventional or experimental diagnostic tests identified pathogens in 42% to 85% of children with community-acquired pneumonia.[1–10] The inconsistent results of these studies arise from variations in study conditions, including the season, geographic location of the study, age of the patients, severity of disease, criteria for admission,

coincidental epidemic of a particular pathogen, and number and type of diagnostic tests performed.

Among the causes of LRIs, *Streptococcus pneumoniae*, although presumed to be the most common bacterial pathogen in most studies, is particularly challenging to diagnose because <10% of children with pneumonia have bacteremia, and there are no definitive tests that are noninvasive and accurate.[2,10–12] Therefore, the epidemiology of LRIs in children remains poorly defined. There is an imperative need for improved diagnostic tests to guide the judicious use of antibiotics as well as to evaluate the effectiveness of currently approved and future vaccines.

We conducted a prospective diagnostic study in the era before routine use of the heptavalent pneumococcal conjugate vaccine to elucidate the etiologic spectrum of community-acquired LRIs among immunocompetent children. The incidence of pneumococcal LRIs was estimated by means of a sensitive and specific pneumolysin-based polymerase chain reaction (PCR) assay that we described previously.[12] Findings from the current study contribute to the limited available data about the epidemiology of LRIs in children, the radiologic characteristics of children with LRIs, and clinical outcome measures in relation to etiologic agents among immunocompetent, hospitalized children. Furthermore, the study provides data that will facilitate age-appropriate antibiotic selection and future evaluation of the clinical effectiveness of the pneumococcal conjugate vaccine as well as other candidate vaccines for LRIs.

METHODS

Study Population

One hundred eighty-four consecutive children with LRIs admitted to Children's Medical Center (Dallas, TX) were evaluated prospectively from January 1999 through March 2000. Children were eligible for enrollment if they were 6 weeks to 18 years old, had preceding fever, and had clinical (tachypnea, chest retractions, or abnormal auscultatory findings) and radiologic evidence of LRI. Children were excluded if they had proven immunodeficiency or immunosuppression or uncomplicated bronchiolitis of presumptive viral etiology. No patients had received the pneumococcal conjugate or polysaccharide vaccines. Subjects were evaluated at enrollment and after 7 to 30 days (median: 14 days), at which time demographic and clinical data were collated uniformly and laboratory specimens were obtained.

The Institutional Review Board of the University of Texas Southwestern Medical Center (Dallas, TX) approved the protocol. Signed informed parental consent and the child's assent (if the child was >10 years old) were obtained.

Radiology

A senior radiologist (N.K.R.), unaware of clinical and laboratory findings, reviewed all chest radiographs. The radiologist assigned standardized and mutually exclusive diagnoses that included unequivocal focal or segmental consolidation with or without pleural effusion, atelectasis, consolidation indistinguishable from atelectasis, or interstitial pneumonia.

Microbiology

A positive bacterial culture from a normally sterile site, viral culture, or direct fluorescent antibody (DFA) test was considered indicative of infection by that organism. Blood cultures were performed with the BacT/Alert 3D system (Organon Teknika, Boxtel, Netherlands) before initiation of parenteral antibiotic therapy among 137 children (89%). When clinically indicated, surgical staff performed diagnostic and therapeutic pleurocentesis by means of video-assisted thoracoscopic surgery[13]; pleural fluid Gram stain and cultures were available for 32 children (21%). Nasopharyngeal swabs for pneumococcal culture were obtained from 135 children (88%) before initiation of parenteral antibiotic therapy, as described previously.[12]

Bartels viral DFA (Trinity Biotech, Carlsbad, CA) and cultures were performed by using naso- and oropharyngeal swabs. The DFA panel could identify respiratory syncytial virus (RSV), adenovirus, parainfluenza 1, 2, and 3, and influenza A and B. In addition to these viruses, cell lines that were used for viral culture (MRC5, monkey kidney, AF549, WI38, and Hep2 cells) could detect rhinovirus and enteroviruses. Patients were screened for pulmonary tuberculosis with Mantoux skin tests by using 5TU purified protein derivative. Gastric aspirate or sputum specimens were subjected to microscopy and culture for mycobacteria when indicated.

Pneumolysin-Based PCR

The methods used for DNA extraction, amplification, and detection were described by us previously.[12] All samples were prepared for storage within 3 hours of collection and frozen at −70°C until tested. Whole blood, buffy coat, and serum samples were obtained from patients within 24 hours of initiation of parenteral antibiotic therapy in 86% of cases and within 48 hours in 92%. A preliminary in vitro study confirmed that the lower limit of detection was <10 colony-forming units/mL. The specificity of buffy coat and whole blood PCR assays among 42 similarly aged control subjects who had no identifiable respiratory disorders was 95% and 100%, respectively. Furthermore, Finnish investigators demonstrated that the same pneumolysin primers had 100% specificity when tested in vitro for a wide variety of pathogens.[14]

Serology

Serum samples were stored at −70°C and subsequently transported on dry ice to the reference laboratories. The laboratory staff was unaware of the clinical data. Concentrations of serum immunoglobulin (Ig)G antibodies to C-polysaccharide and pneumolysin as well as immune complexes containing the same antibodies were measured by enzyme immunoassay (by M.L.) in Oulu, Finland as described previously.[12]

Serologic tests for *Chlamydia pneumoniae* and *Chlamydia trachomatis* were performed in Oulu, Finland (by M.L.) by using microimmunofluorescence with Kajaani 6 antigen for *C pneumoniae* and L2 antigen for *C trachomatis* to detect IgM, IgG, and IgA titers; acute infection was indicated by a ≥4-fold rise in IgG or IgA titers or an IgM titer ≥1:16.[15,16] In addition, an enzyme immunoassay was performed for *C pneumoniae* according to manufacturer instructions (Labsystems, Helsinki, Finland).

Mycoplasma pneumoniae enzyme-linked immunosorbent assays were performed (by L.B.D.) in Birmingham, Alabama. The assay was considered positive if the IgM was ≥1:10 or there was a ≥4-fold rise in IgG titer.[17]

Viral enzyme immunoassays performed in Turku, Finland (by T.Z.) included assays for RSV, adenovirus, parainfluenza 1, 2, and 3, and influenza A and B. A ≥4-fold increase in IgG titer was indicative of acute viral infection.

Inflammatory Indices

An automated white blood cell (WBC) count with manually verified differential count was performed in 138 children (90%). Serum procalcitonin concentrations were measured in 150 children (97%) as described previously.[12]

Treatment

All patients were treated with a sequential parenteral and oral antibiotic regimen for presumed bacterial LRI. The antimicrobial agent of choice for uncomplicated LRI was cefuroxime for a duration of 10 to 14 days. Alternative or additional agents were used at the discretion of the attending physician.

Statistics

Statistical analyses were performed with SPSS for Windows 10.0 (SPSS Inc, Chicago, IL). Categorical variables were compared with Yates' corrected χ^2 or Fisher's exact tests when appropriate. Skewed continuous variables were transformed by using natural logarithms when possible and compared by 1-way analysis of

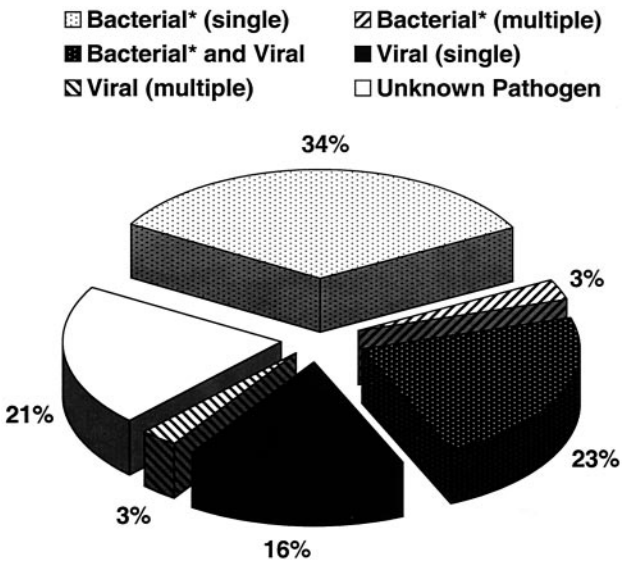

Fig 1. Etiology of LRIs in 154 hospitalized children. Pneumococcal disease was detected by blood or pleural fluid cultures or PCR assays. The asterisk denotes typical respiratory bacterial pathogens (*M pneumoniae*, *C pneumoniae*, and *M tuberculosis*).

variance tests or by Kruskal-Wallis and Mann-Whitney *U* tests when appropriate. Posthoc multiple comparisons were performed to determine the origins of significant differences, and the results were adjusted by using the Bonferroni method. Backward stepwise logistic-regression analyses were performed to determine the best predictors of culture- or PCR-positive bacterial pneumonia. Covariates included in the regression model were age, maximum temperature within 72 hours after admission, wheeze, duration of hospitalization, pleural effusion, band forms, and procalcitonin concentration. The radiologic finding of consolidation (with or without pleural effusion) was omitted from the regression model because of colinearity between this variable and pleural effusion. All statistical tests were 2-sided. Statistical significance was defined as $P < .05$.

RESULTS

Patients

One hundred fifty-four children with LRIs met the inclusion criteria for enrollment. Of these patients, 96 (62%) were male. Ages ranged from 2 months to 17 years (median: 33 months). Eight percent were <6 months old, 31% were 6 months to <2 years old, 30% were 2 to <5 years old, and 31% were ≥5 years old. Rates of admission of African American (36%), Hispanic (29%), and white (29%) children were similar to general hospital admission rates. Sixty-one children (40%) had received oral antibiotic therapy within the preceding 2-week period. Many patients had comorbidities: 30 children (20%) had ≥1 previous episode of reactive airway disease, 8 had identifiable genetic syndromes, and 6 had neurocognitive disorders. The median duration of symptoms before admission was 5 days, and the mean temperature at admission was 39.2°C. The median duration of hospitalization was 5 days. Ninety-three children (60%) received supplemental oxygen therapy for a median of 3 days. Ten children required assisted ventilation, and 2 of them died from complications of pneumococcal or group A streptococcal sepsis and pneumonia.

Etiology

At least 1 respiratory pathogen was identified in 79% (122 of 154) of the patients. As reported previously, there was poor concordance between pneumococcal PCR and serologic assay results.[12] Nevertheless, a combination of these tests identified only 5 additional children with acute pneumococcal infection, and because serologic methods have not been validated sufficiently for use in children, we used only blood and pleural fluid cultures and PCR assays as the reference standards to diagnose pneumococcal disease in the current study.

The risk of LRIs attributable to identifiable pathogens is shown in Fig 1. Bacteria with or without coinfecting pathogens were identified in 60% of cases overall (93 of 154 children). Pneumococcal disease was confirmed in 68 children (44% overall, 73% of patients with documented bacterial disease; Table 1). Bacteria included typical respiratory pathogens (*S pneumoniae*, *Streptococcus pyogenes*, *Streptococcus milleri*, and *Staphylococcus aureus*), atypical respiratory agents (*M pneumoniae* in 14% of children and *C pneumoniae* in 9%; Table 1), and *Mycobacterium tuberculosis*. Pathogenic organisms were isolated from 11

TABLE 1. Pathogens Identified in 154 Hospitalized Children with Community-Acquired LRIs

Pathogen	No. of Episodes			Total No. of Episodes, %
	No Coinfection	Coinfection With Bacteria*	Coinfection With Viruses*	
Bacteria				
S pneumoniae	35	12	21	68 (44)
S pyogenes	0	2	2	2 (1)
S aureus	0	2	0	2 (1)
S milleri	0	1	1	1 (<1)
M pneumoniae	11	6	8	21 (14)
C pneumoniae	6	7	7	14 (9)
M tuberculosis	1	1	0	2 (1)
C trachomatis	0	0	0	0
Viruses				
Influenza A or B	9, 1	16, 6	10, 6	26 (17), 7 (5)
RSV	6	11	8	20 (13)
Parainfluenza 1–3	6	12	10	20 (13)
Adenovirus	2	9	5	11 (7)
Rhinovirus	1	2	2	5 (3)
Enteroviruses	0	1	0	1 (<1)

* The categories of coinfection with bacteria and with viruses are not mutually exclusive.

TABLE 2. Demographic and Clinical Characteristics of 154 Hospitalized Children With Community-Acquired LRIs Associated With Bacterial, Viral, or Unknown Pathogens

Characteristics	Type of Lower Respiratory Pathogens					*P* Value
	Typical Bacteria[a]	*M pneumoniae* or *C pneumoniae*[b]	Viruses[c]	Mixed Bacteria/ Viruses[d]	Unknown	
No. of patients, %	40 (26)	17 (11)	29 (19)	36 (23)	32 (21)	
Age, mo (range)[e]	39.5 (2.3–209)	60.2 (9–155)[f]	18.5 (2.2–194)[fg]	27.6 (2–134)	41.4 (4–158)[g]	.015
Age <5 y, %	70	47	76	78	63	.17
Gender, % male	73[f]	47	69	44[f]	72	.04
Duration of symptoms before admission, days[e]	6.0	3.5	7.0	5.0	4.0	.41
Antibiotic therapy during preceding 2 weeks, %	33	24	55	44	38	.20
Temperature on admission, °C[h]	39.4	39.1	39.0	39.2	39.1	.46
Maximum temperature ≤72 hours after admission, °C[h]	38.4[fg]	37.5[gi]	37.6[fj]	38.5[ij]	37.9	.001
Wheeze, %	13[f]	41	41[fg]	14[g]	31	.01
Lobar or segmental consolidation ± effusion, %	75	53	45	69	53	.06
Pleural effusion, %	50[fgj]	6[f]	10[g]	39	19[j]	.0002
WBC count, × 10^9/L[e]	16.1	12.3	14.5	15.6	14.4	.76
Band forms, %[e]	6.5	1.5[f]	1.0[g]	11.5[fg]	3.0	.038
Band forms (proportion >10%)	39	8[f]	27	56[fg]	19[g]	.006
S pneumoniae NP colonization, %	20	12	35	22	22	.48
Procalcitonin, ng/mL[e]	2.4[f]	0.7[fg]	0.6[j]	2.6[gj]	1.3	.014
Procalcitonin, proportion ≥0.75 ng/mL	68[f]	41	32[fgj]	66[g]	67[j]	.012
Paired serum available, %	78	82	79	94	69	.08
Macrolide/azalide included in regimen, %	8	18	17	11	22	.44
Duration of oxygen therapy, days[e]	1.2	1.0	1.8	2.0	1.8	.28
Duration of hospitalization, % >5 days[ek]	62[fg]	24[f]	31	59[j]	23[gj]	.001
No. ventilated/died/readmitted within 30 days of discharge	1/0/0	1/0/0	3/0/1	3/2/2	2/0/1	ND

NP indicates nasopharyngeal; ND, not done (sparse data).
[a] Typical respiratory pathogens included *S pneumoniae, S pyogenes, S milleri, S aureus,* and *M tuberculosis*. This category included children with mixed typical bacterial infections as well as 3 patients acutely coinfected with *M pneumoniae* ($n = 2$) or *C pneumoniae* ($n = 1$).
[b] Eleven children had *M pneumoniae* infections only, and 6 had *C pneumoniae* infections only. Ten additional children with *M pneumoniae* were coinfected with other bacteria or viruses, and 8 additional children with *C pneumonaie* were coinfected with other bacteria or viruses. Patients infected with atypical bacterial pathogens who had concurrent typical bacterial infections were classified as "typical bacteria," and those coinfected with viruses were categorized as "mixed bacterial/viral." Median age and range for all *M pneumoniae* cases ($n = 21$) was 60 months (6–148 months) and for all *C pneumoniae* cases ($n = 14$) was 35 months (7–155 months).
[c] The viral category included children with single or multiple concurrent viral pathogens.
[d] The mixed bacterial/viral category included patients with combinations of typical or atypical respiratory bacteria and viral pathogens.
[e] The median value was used.
[f] Significant differences were observed between each pair of values.
[g] Significant differences were observed between each pair of values.
[h] The mean value was used.
[i] Significant differences were observed between each pair of values.
[j] Significant differences were observed between each pair of values.
[k] Four patients with prolonged admissions for social indications were omitted.

(34%) of 32 pleural fluid samples (*S pneumoniae*: 6 patients; *S pyogenes*: 2; *S aureus*: 2; *S milleri*: 1). Thirty-four patients (22%) were acutely infected with *M pneumoniae* or *C pneumoniae* with or without other coinfecting pathogens, and 50% of these patients (17 children) had no other coinfecting pathogens (Table 2).

Overall, 65 of 143 evaluable children (45%) had viral infections. Influenza A, RSV, and parainfluenza 1, 2, and 3 were the most common viruses (Fig 2). Notably, serologic assay, viral culture, and DFA results identified combinations of 2 to 4 viruses that coinfected 16 patients (11%). Mixed bacterial/viral infections occurred in 23% of children.

The proportion of children with identifiable pathogens decreased with increasing age (Fig 3). Etiologic diagnoses were documented in 92% of infants <6 months old, whereas only 75% of children >5 years old had detectable pathogens. Similarly, the proportion of identifiable viral infections decreased with increasing age, whereas bacterial infections increased with age (Fig 3). These results were not affected by the availability of convalescent serum samples among children in each age group ($P = .22$). The variations in incidence of pathogens during 12 consecutive months are shown in Fig 4; the peak incidence of LRIs occurred during January through April.

Comparative Clinical and Radiologic Data

The demographic and clinical characteristics of the patients by infection type are shown in Table 2. The ages of children infected with only *M pneumoniae* or

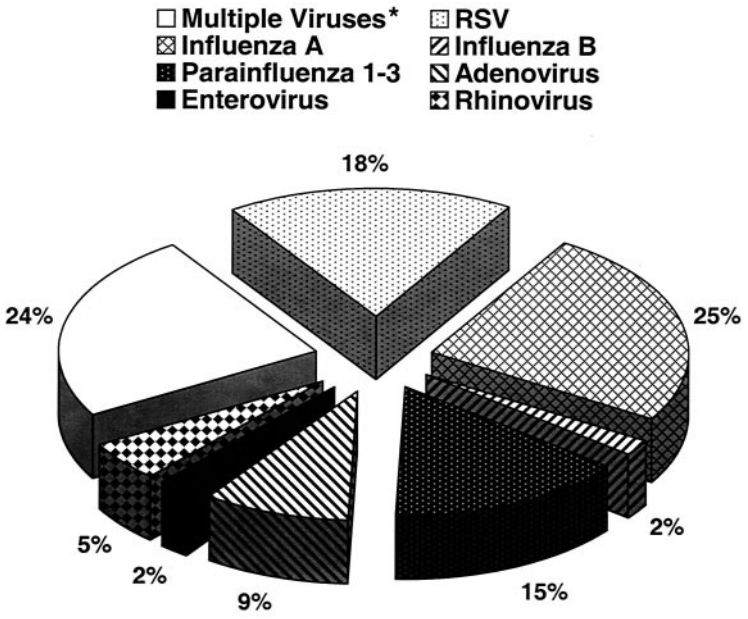

Fig 2. Distribution of viruses associated with pneumonia. Viruses were identified in 65 (45%) of 143 evaluable children hospitalized with LRIs. The asterisk indicates combinations of 2 to 4 viruses that were identified in 16 (11%) of 143 children.

C pneumoniae ranged from 9 months to 13 years old, but, notably, 47% of these children were <5 years old. Their median age (60 months) was significantly greater than that of children infected with only viruses (18 months). The duration of symptoms and utilization of antibiotics preceding admission was similar among all groups of patients. The proportion of children presenting with wheezing was greatest among children with viral and atypical respiratory pathogens. The type of infection was not associated with total WBC count or pneumococcal nasopharyngeal colonization.

Univariate analyses of laboratory and clinical data suggested that the children with mixed bacterial/viral infections as well as those with only typical respiratory bacterial pathogens had the greatest inflammation and disease severity, as evidenced by high temperature (≥38.4°C) within 72 hours after admission, association with pleural effusions, high percentage of band forms, elevated levels of procalcitonin, prolonged hospitalization, and a relatively high proportion of patients requiring assisted ventilation and readmission to hospital (Table 2). These data were not influenced significantly by rates of follow-up, presence of nasopharyngeal colonization with *S pneumoniae*, or treatment with a macrolide or azalide antibiotic during hospitalization. Univariate analysis of differences in consolidation (with or without effusion) among groups trended toward significance ($P = .06$; Table 2). These differences were significant after the etiologic categories were collapsed into bacterial (typical and atypical) versus viral infections or bacterial (typical) versus viral and atypical bacterial infections ($P = .03$ and .01, respectively; Yates' corrected χ^2 tests). However, the findings should be interpreted with caution because of significant correlation between the covariates, consolidation (with or without pleural effusion), and pleural effusion (ϕ coefficient: .5; $P < .001$).

Multivariate logistic-regression analyses revealed that only 2 variables were associated with bacterial pneumonia: high temperature (≥38.4°C) within 72 hours after admission (odds ratio: 2.2; 95% confidence interval: 1.4–3.5) and presence of pleural effusion (odds ratio: 6.6; 95% confidence interval: 2.1–21.2). The proportion of explained variance of the

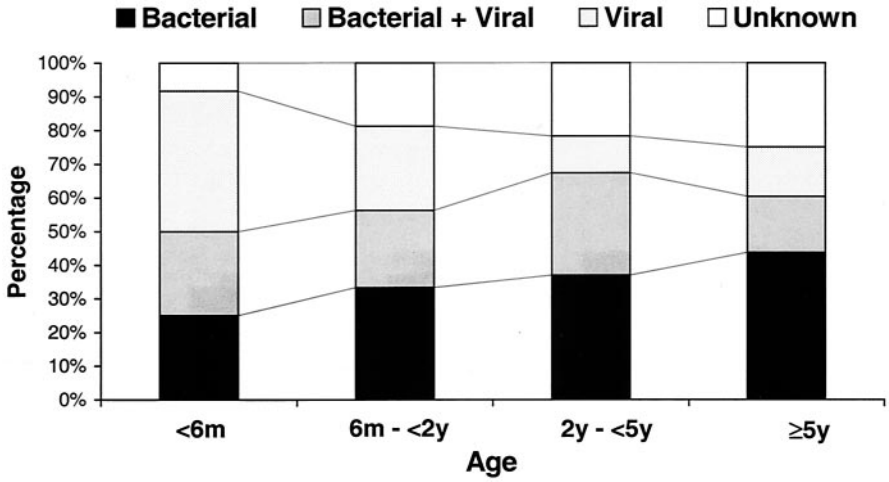

Fig 3. Distribution of pathogens associated with LRIs, stratified by age.

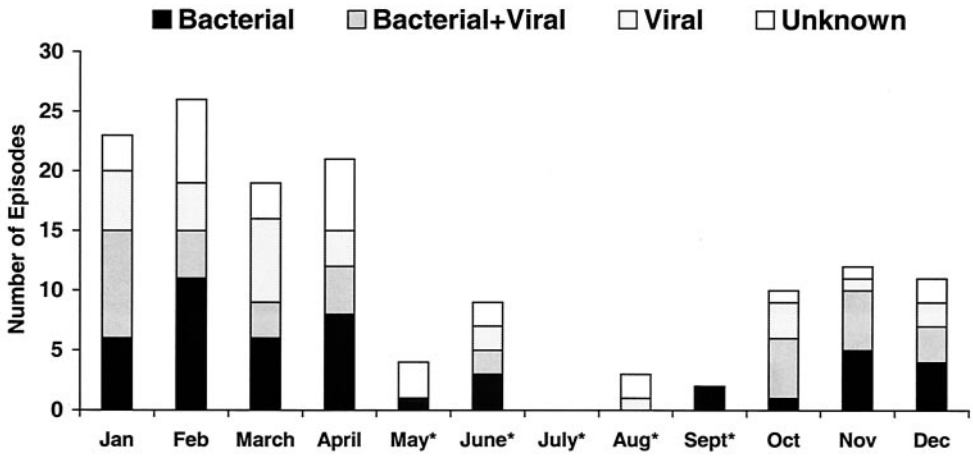

Fig 4. Distribution of pathogens associated with LRIs during 12 consecutive months (January through December 1999). The asterisk refers to pathogens identified during the summer months: *S pneumoniae* ($n = 5$), RSV ($n = 4$), parainfluenza 1, 2, and 3 ($n = 4$), *M pneumoniae* ($n = 2$), and *C pneumoniae* ($n = 1$).

model was 33% (Nagelkerke R^2). The sensitivity of the model was 79%, and the specificity was 59%.

DISCUSSION

One hundred fifty-four immunocompetent children hospitalized for the treatment of acute community-acquired pneumonia were studied prospectively to elucidate the epidemiology of LRIs and clinical outcomes of disease. A comprehensive investigation combining microbiologic, serologic, biochemical, and experimental molecular tests was undertaken to maximize the diagnostic yield. Overall, a pathogen was identified in 79% of children. Bacteria accounted for 60% of infections, of which 73% were caused by *S pneumoniae*. *M pneumoniae* and *C pneumoniae* were detected in 14% and 9% of all cases, respectively. Viruses were documented in 45% of children. Notably, 23% of the children had concurrent acute viral and bacterial disease.

We showed that children with typical respiratory bacterial pathogens as well as those with mixed bacterial and viral LRIs had the greatest degree of inflammation and disease severity, as evidenced by high temperature after admission, positive association with pleural effusion, high percentage of band forms, elevated procalcitonin values, prolonged hospitalization, and tendency to require assisted ventilation and readmission to hospital. Specifically, the 2 clinical features that were most strongly associated with bacterial pneumonia were high temperature (≥38.4°C) within 72 hours after admission and presence of pleural effusion. However, because the decision to initiate antibiotic therapy is made typically at the time of admission, the subsequent fever pattern is not clinically useful. Conversely, the current study indicates that, at the time of admission, the temperature, the total WBC count, the presence of pneumococcal nasopharyngeal colonization, and radiographic findings in the absence of pleural effusion cannot distinguish the causes of LRIs accurately. Children with proven viral infections tended to be younger and wheezed more frequently than children with bacterial or mixed bacterial/viral infections. Children with *M pneumoniae* and *C pneumoniae* infections had median ages of 5 years (range: 6 months to 12 years) and 35 months (range: 7 months to 13 years), respectively, indicating that preschool-aged children have at least as many episodes of atypical respiratory LRIs as older children. These findings corroborate those of previous studies.[5,18]

Our inability to attribute all episodes of LRIs in children to known pathogens likely resulted from a combination of clinical and technical limitations such as administration of antibiotic therapy before acquisition of fluid samples, absence of specific tests for *Moraxella catarrhalis*[19] and *Haemophilus influenzae*,[20] absence of convalescent serology in 21% of patients, and inability to identify novel pathogens such as metapneumovirus that accounted for 8% of cases of wheezing with or without pneumonia among Finnish children.[21]

Etiologic data from the current study corroborated findings of other investigators.[5,10,22] Furthermore, the attributed role of *S pneumoniae* was documented in 44% of the cases. Although this proportion is higher than that found in other reports, our finding is consistent with the protective efficacy of the pneumococcal conjugate vaccine that was shown to reduce the incidence of radiographically documented pneumonia by 23% in the first 2 years of life and 32% in the first year of life. Overall, the efficacy of the pneumococcal conjugate vaccine was ~20%.[23]

Previous reports of mixed bacterial/viral LRIs in children were confirmed in the current study in which approximately one quarter of cases had concurrent infections.[10,18,24] Furthermore, significant proportions of children had dual bacterial or viral LRIs. Clinical and laboratory findings from the current and previous studies raise the important question of whether sequential or concurrent viral and bacterial infections have a synergistic impact on the evolution of disease in children.[25]

Generally accepted national consensus statements and individuals' recommendations for treatment of community-acquired pneumonia in children are based on available evidence that ranges from informal expert opinion to well-designed prospective studies.[26–28] Notably, there is no national consensus

on treatment for childhood pneumonia in the United States. However, even the most rigorous efforts to define the epidemiology of pneumonia in children are limited by the paucity of validated data. Therefore, accurate characterization of the causes of LRIs is essential to guide appropriate antibiotic utilization. This is the first pediatric study to identify the broad spectrum of diseases and overlapping contributions by coinfecting pathogens that cause pneumonia by successfully combining conventional and molecular tests in an expanded diagnostic armamentarium.

CONCLUSIONS

Bacteria accounted for the majority of identifiable infections in immunocompetent children hospitalized with pneumonia in this series. Mixed bacterial/viral infections occurred in one quarter of the cases, and no clinical, radiologic, or laboratory features distinguished these cases from others with single infections. The only clinical characteristics that were significantly associated with bacterial pneumonia were high temperature (≥38.4°C) within 72 hours after admission and the presence of pleural effusion. Therefore, antibiotics directed against common, typical bacterial respiratory pathogens are warranted, at least initially, to reduce morbidity and possibly mortality associated with pneumonia in hospitalized children. On the other hand, although the current study was not designed to measure the effectiveness of antibiotic therapy, there was no evidence to suggest improved outcome among children who were infected with *M pneumoniae* or *C pneumoniae* and who were treated with macrolide or azalide antibiotics.[29] Future prospective intervention studies are warranted to define the role of antibiotic therapy for atypical respiratory infections and to determine appropriate therapeutic options for pneumonia in children who have received a full series of the pneumococcal conjugate vaccine.

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