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Clinical Features and Outcomes of Community-Acquired Pneumonia Caused by *Haemophilus influenzae*

Saeed Shoar,[1,2] Fernando H. Centeno,[1,2] and Daniel M. Musher[1,2]

[1]Baylor College of Medicine, Houston, Texas, USA, and [2]Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA

Background. Long regarded as the second most common cause of community-acquired pneumonia (CAP), *Haemophilus influenzae* has recently been identified with almost equal frequency as pneumococcus in patients hospitalized for CAP. The literature lacks a detailed description of the presentation, clinical features, laboratory and radiologic findings, and outcomes in *Haemophilus* pneumonia.

Methods. During 2 prospective studies of patients hospitalized for CAP, we identified 33 patients with *Haemophilus* pneumonia. In order to provide context, we compared clinical findings in these patients with findings in 36 patients with pneumococcal pneumonia identified during the same period. We included and analyzed separately data from patients with viral coinfection. Patients with coinfection by other bacteria were excluded.

Results. *Haemophilus* pneumonia occurred in older adults who had underlying chronic lung disease, cardiac conditions, and alcohol use disorder, the same population at risk for pneumococcal pneumonia. However, in contrast to pneumococcal pneumonia, patients with *Haemophilus* pneumonia had less severe infection as shown by absence of septic shock on admission, less confusion, fewer cases of leukopenia or extreme leukocytosis, and no deaths at 30 days. Viral coinfection greatly increased the severity of *Haemophilus*, but not pneumococcal pneumonia.

Conclusions. We present the first thorough description of *Haemophilus* pneumonia, show that it is less severe than pneumococcal pneumonia, and document that viral coinfection greatly increases its severity. These distinctions are lost when the label CAP is liberally applied to all patients who come to the hospital from the community for pneumonia.

Keywords. clinical characteristics; community-acquired pneumonia; *Haemophilus* pneumonia; pneumococcal pneumonia.

Since our initial description of pneumonia due to nontypeable *Haemophilus influenzae* in 1983 [1], this organism has increasingly been recognized as the second most common bacterial cause of community-acquired pneumonia (CAP), only exceeded in frequency by *Streptococcus pneumoniae* [2]. In fact, 2 recent reports that were based on quantitative studies of high-quality sputum, 1 molecular [3] and the other bacteriologic [4], found that *Haemophilus* and pneumococcus were about equally prominent as etiologic agents of CAP, far exceeding other bacterial causes.

Whereas ample clinical data have been presented for patients with pneumococcal pneumonia, including all cases [5–8], only severe cases [9], and only bacteremic (invasive) cases [10–13], information on the clinical presentation and manifestations of *Haemophilus* pneumonia has been surprisingly limited [1, 14–16]. Given the well-documented medical and societal importance of CAP [17, 18], we felt that a detailed description of pneumonia due to *H. influenzae* was appropriate. The purpose of the present study was to provide such a description.

METHODS

Subjects

Patients in this report were identified prospectively as part of 2 previous studies. Study 1 was a 1-year prospective study of the etiology of CAP that included every patient admitted to the Michael E. DeBakey VA Medical Center (MEDVAMC) with this diagnosis from July 5, 2011 to June 30, 2012 [19]. Study 2 was a continuation of an earlier prospective convenience series of patients hospitalized at MEDVAMC for CAP between September 21, 2017 and January 31, 2020, who were included if they were able to provide a high-quality sputum sample, defined by the presence of ≥20 polymorphonuclear leukocytes (PMNs) per epithelial cell at or soon after admission [4].

For both studies, CAP was defined as the radiologic documentation of a newly recognized pulmonary infiltrate with ≥2 of the following findings: fever, increased cough, sputum production, shortness of breath, pleuritic chest pain, rales, or confusion. Laboratory studies included sputum and blood cultures, polymerase chain reaction (PCR) for respiratory viruses, *Mycoplasma* and *Chlamydia* on a nasopharyngeal swab, and urine antigen for *S. pneumoniae* and *Legionella* in ~95% of cases. For Study 2, patients were required to submit a sputum

sample within 16 hours of antibiotics being begun; 65% of the samples were obtained before or within 2 hours after the first antibiotic dose. Patients whose sputum contained more than 1 bacterial respiratory pathogen were excluded from the analysis.

As we were tabulating data on patients with *Haemophilus* pneumonia, we realized that a useful context for comparison might be provided by comparing these results with those from patients in the same data set who had pneumococcal pneumonia. Accordingly, in the present paper, we present and contrast data on patients from Studies 1 and 2, comparing results in *Haemophilus* and pneumococcal pneumonia.

These studies were approved by the Institutional Review Board, Baylor College of Medicine, and the Research and Education Committee, MEDVAMC.

Data

The electronic medical record was used to obtain demographic information, medical history, physical findings, and admitting imaging and laboratory studies. After tabulating results for patients with *Haemophilus* pneumonia, we compared them with those for patients with pneumococcal pneumonia. Subanalyses were done to examine the effect of viral coinfection.

Statistics

Data were analyzed using the Statistical Package for the Social Sciences (version 16.0; SPSS Inc.). The Kolmogorov-Smirnov normality test was used to assess the distributional form of continuous variables. If they were normally distributed, the Student t test was used to compare them; otherwise, the Mann-Whitney U test was applied. Categorical variables were compared using the chi-square test. Continuous data are presented as mean ± SD if normally distributed or median (interquartile range) if not. Statistical significance was set at $P \le .05$.

RESULTS

Thirty-three patients had pneumonia due to *H. influenzae,* and 36 had pneumonia due to *S. pneumoniae*, illustrating the nearly equal prominence of these 2 bacteria as etiologic agents of CAP in our tertiary care hospital. As shown in Table 1, 90.9% of *Haemophilus* pneumonia patients were current (54.5%) or former (36.4%) smokers, and 78.8% had chronic pulmonary disease. Alcohol use disorder (33.3%), diabetes mellitus (30.3%), and heart disease (69.6%) were prominent. Comparison of demographic factors and comorbid conditions (Table 1) revealed a striking similarity between patients with *Haemophilus* pneumonia and those with pneumococcal pneumonia, except for the greater percentage of patients in the *Haemophilus* group who had chronic kidney disease. This also included the rate of vaccination with 23-valent pneumococcal polysaccharide vaccine.

The usual presenting symptoms of pneumonia (increased cough, sputum production, and shortness of breath) were present in >75% of patients with *Haemophilus* pneumonia.

Table 1. Demographic Factors and Comorbid Conditions, Patients With CAP due to *H. influenzae* Compared With CAP due to *S. pneumoniae*[a]

	H. influenza (n = 33)	*S. pneumonia* (n = 36)	*P* Value
Age, mean±SD, y	69.4±10	68.7±8.5	.8
Gender (male:female), No.	31:2	35:1	.5
Race			.5
White	66.7	63.9	
Black/African American	27.3	33.3	
Other	6	2.8	
Long-term care facility	6.1	5.6	.9
Smoking status			.4
Current	54.5	38.9	
Former	36.4	44.4	
Never	9.1	16.7	
Alcohol use disorder	33.3	36.1	.9
Chronic obstructive pulmonary disease	60.6	44.4	.2
Other chronic respiratory conditions	18.2	19.4	.9
Congestive heart failure	24.2	13.9	.3
Other heart disease	45.4	38.9	.6
Diabetes mellitus	30.3	22.2	.4
Glycated hemoglobin >7.5%	9.1	2.8	.3
Stroke	18.2	19.4	.9
Chronic kidney disease	15.2	0	.02
Autoimmune disease	3	5.6	.6
Cirrhosis	3	11.1	.2
Hepatitis C	21.1	16.7	.6
HIV	9.1	8.3	.9
Immunosuppressed	12.1	11.1	.9
Malnutrition	24.2	19.4	.6
Homelessness	9.1	5.6	.6
Neurological disorder	6.1	5.6	.9
History of malignancy	15.2	30.6	.1
Pneumococcal vaccination within 10 y	69.7	61.1	.4

Abbreviation: CAP, community-acquired pneumonia.

[a]Categorical variables are presented as percentage. Continuous variables are presented as median and interquartile range.

Subjective fever (42.4%) and pleuritic chest pain (27.3%) were less commonly present. At admission, 78.8% of patients with *Haemophilus* pneumonia had a recorded temperatures <99.4°F. Pneumonia was multilobar in 57.6% of the cases with *Haemophilus*. Abnormalities on electrocardiogram and troponin I >0.03 ng/mL were detected in 30.0% and 81.8%, respectively. Similar results were observed in patients with pneumococcal pneumonia (Table 2).

In contrast, nearly all markers of acuity of infection appeared to be less prominent in patients with *Haemophilus* than in those with pneumococcal pneumonia. At admission, mean and median temperatures were significantly lower in those with *Haemophilus* than in those with pneumococcal pneumonia ($P < .05$ for both comparisons) (Table 2). Median pulse (88 vs 103; $P = .08$) and respiratory rate (18 vs 20; $P = .1$) tended to be lower, as did the presence of altered mentation (6.1% vs 22.2%; $P = .06$). One patient (3.0%) with *Haemophilus* pneumonia had a white blood cell (WBC) count <6000/mm^3, and none had

Table 2. Clinical, Laboratory, and Radiologic Findings at Admission, Patients With CAP due to *H. influenzae* Compared With CAP due to *S. pneumoniae*[a]

Findings at Admission	*H. influenzae* (n = 33)	*S. pneumoniae* (n = 36)	*P* Value
Subjective fever	42.4	55.6	.3
Rigors/chills	39.4	41.7	.8
Increased cough	87.9	88.9	.9
Shortness of breath	87.9	75	.2
Increased sputum production	75.8	66.7	.4
Pleuritic chest pain	27.3	22.2	.6
Hemoptysis	3	2.8	.9
Diarrhea	9.1	5.6	.6
Headache	3	5.6	.6
Upper respiratory symptoms	39.4	38.9	1.0
Myalgia	9.1	5.6	.6
Temperature	98.3 [97.8–99.2]	98.9 [98.03–100.7]	.02
Temperature ≥99.4°F	21.2	36.1	.2
Heart rate	88 [74–111]	103 [89.2–113.7]	.08
Respiratory rate	18 [18–22]	20 [18–22]	.1
Altered mentation	6.1	22.2	.06
Multilobar involvement in chest imaging	57.6	47.2	.4
New pleural effusion in chest imaging	15.2	25	.3
Intubation	18.2	13.9	.6
O2 saturation, %	92 [88–94]	93 [85–97]	.6
White blood cell count ≤6000, cells/mm^3	3	11.1	.2
White blood cell count ≥11 000, cells/mm^3	34.8	33.3	.4
White blood cell count ≥25 000, cells/mm^3	0	8.3	.09
Band forms ≥6%	0	8.3	.09
Hemoglobin, g/dL	12.3 [11.05–14.25]	12.9 [11.2–14.02]	.7
Platelets, cells/mm^3	252k [194k–336k]	243k [186k–364k]	.8
Creatinine, mg/dL	1.13 [0.9–1.52]	1.01 [0.87–1.35]	.2
Albumin, g/dL	3.1 [2.7–3.5]	3.15 [2.7–3.4]	.7
Creatine kinase (MB), IU/L	4.3 [2.5–6.9]	3.2 [1.8–5.8]	.3
Troponin I ≥0.03, ng/mL	81.8	66.7	.15
New EKG abnormality	30	33.3	.8
Brain natriuretic peptide, pg/mL	166 [101.2–415.2]	144 [75–321]	.5
Positive blood culture	0	16.7	.01
Viral coinfection	21.2	25	.6
Viral type			.5
Human metapneumovirus	0	11.1	
Influenza A	42.9	22.2	
Parainfluenza 3 RP	14.3	0	
Rhinovirus	28.6	33.3	
Respiratory syncytial virus	14.3	33.3	

Abbreviations: CAP, community-acquired pneumonia; EKG, electrocardiogram; MB, Membrane-based; RP, Respiratory panel.

[a]Categorical variables are presented as percentage. Continuous variables are presented as median and interquartile range.

>25 000 WBC/mm^3, compared with 4 (11.1%) and 3 (8.3%), respectively, with pneumococcal pneumonia (*P* for each value > .05). However, when counted together, patients with *Haemophilus* pneumonia were significantly less likely to have <6000/mm^3 or >25 000 WBC/mm^3 compared with patients with pneumococcus pneumonia (*P* = .03). No *Haemophilus* patient had >6% band forms, compared with 8.3% of those with pneumococcus (*P* = .09). Blood cultures were uniformly negative in patients with *Haemophilus* pneumonia, whereas 6 of 36 (16.7%) patients with pneumococcal pneumonia were bacteremic (*P* = .01).

Although the rate of admission to the intensive care unit (ICU) was the same in both groups (Table 3), a significantly lower proportion of patients with *Haemophilus* pneumonia were in shock at admission (0% vs 13.9%; *P* = .03). *Haemophilus* patients also tended to have lower qSOFA scores and pneumonia severity indices (*P* = .1 for each comparison). At 30 days, there were no deaths in the *Haemophilus* group compared with 5 (13.9%) in the pneumococcal group (*P* = .02).

Similar proportions of patients with *Haemophilus* and pneumococcal pneumonia (21.2% and 25.0%, respectively) had a viral coinfection. The frequency of viruses responsible for

Table 3. Severity of Infection in Patients With CAP due to *H. influenzae* Compared With CAP due to *S. pneumoniae*[a]

	H. influenzae (n = 33)	*S. pneumoniae* (n = 36)	P
Shock	0	13.9	.03
Admission to ICU	15.2	16.7	.9
PORT score	92 [81–118]	100.5 [86–130.75]	.2
Pneumonia Severity Index	4 [3–4]	4 [3–4]	.1
ATS/IDSA severe pneumonia	18.2	16.7	.9
qSOFA ≥2	3	13.9	.1
In-hospital mortality	0	11.1	.05
30-d mortality	0	13.9	.02

Abbreviation: ATS, American Thoracic Society; CAP, community-acquired pneumonia; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; PORT, Pneumonia Patient Outcomes Research Team; qSOFA, quick Sequential Organ Failure Assessment.

[a]Categorical variables are presented as percentage. Numeric variables are presented as median and interquartile range.

the viral coinfection was similar between the 2 groups. Viral coinfection significantly worsened some measures of disease severity in patients with *Haemophilus* pneumonia but had no impact on the severity of infection in pneumococcal pneumonia (Table 4). For example, no patients with pure *Haemophilus* CAP required ICU admission, compared with 14.3% of the patients with *Haemophilus* pneumonia and a viral coinfection. In contrast, viral coinfection did not significantly increase the need for ICU admission in patients with a pneumococcal CAP.

DISCUSSION

A systematic review of the etiology of CAP has shown that *S. pneumoniae* and *H. influenzae* are the most commonly identified bacterial causes of CAP [2]. Our results, obtained prospectively, show that, in fact, at the present time and in a veteran population, these 2 organisms cause CAP in nearly equal proportions, results similar to those obtained by Gadsby et al. in the general population [3]. Increased recognition of *Haemophilus* relative to pneumococcus as a cause of CAP in the United States is probably attributable to the general decline in pneumococcal pneumonia among adults, a decline noted since early in the antibiotic era [20] but undoubtedly hastened by the indirect protective effect in adults of widespread use of conjugate pneumococcal vaccine in infants and children [21]. Consistent with previous reports [1, 14–16], the incidence of comorbid conditions among patients with *Haemophilus* pneumonia was high, especially chronic lung disease, cigarette smoking, heart disease, and alcohol use disorder, but no apparent differences in demographic features or underlying comorbid conditions distinguished *Haemophilus* from pneumococcal pneumonia.

In contrast, by nearly every criterion of severity, pneumonia due to *Haemophilus* appeared to be less severe than that caused by pneumococcus. At admission, *Haemophilus* patients were significantly less likely to have altered mental status. None was in shock, and none died. WBC counts <6000 or >25 000/mm^3 and band forms >6% and well-documented markers of severity in pneumonia [22, 23], occurred nearly exclusively in pneumococcal patients. The similar rates of ICU admission may have

been due to underlying lung disease: 60.6% of *Haemophilus* pneumonia patients had been diagnosed with COPD compared with 44.4% of patients with pneumococcal pneumonia (difference not significant, P = .2), but we do not have data on the severity of the underlying lung disease in the 2 groups.

To our knowledge, no previous study has described the clinical presentation of *Haemophilus* pneumonia in this detail or has compared its clinical severity with other bacterial causes of pneumonia [1, 14–16]. The tendency to lump all pneumonias under the rubric of CAP hides the fact that there are real distinctions based on specific etiologic agents. Our documentation of a greater severity of pneumococcal than *Haemophilus* pneumonia supports earlier work by Restrepo et al. [24], who showed that, in patients with CAP, *H. influenzae* caused 13.3% of ward admissions and 5.3% of ICU admissions, whereas for pneumococcal pneumonia these numbers were 31.7% and 38.6%, respectively.

Data presented by Kofteridis et al. [15] and Sanchez et al. [16] suggested a higher acuity of *Haemophilus* pneumonia than in the present series, but 42% of the cases of Kofteridis et al. were due to type b or type e infection, and a substantial proportion of patients reported by Sanchez et al. had coinfection with other bacteria, rendering comparisons difficult. In our series, the high frequency of underlying lung disease (63.8%) was consistent with all previous reports (60%–80% of cases) [1, 14–16] and higher than that reported for pneumococcal pneumonia (13.5%–50%) [6, 7, 11, 25]. The greater rate of multilobar involvement in our cases of *Haemophilus* pneumonia (57%) than previously reported [1, 16] is likely due to increased use of routine chest CT. The rate of pleural effusion in our study was similar to that reported previously for *Haemophilus* pneumonia [1, 15, 16], as was the infrequency of bacteremia [1, 15, 16] and the absence of death due to infection [1, 16].

A novel finding of our study is that viral coinfection rendered *Haemophilus* pneumonia substantially more severe without affecting the severity of pneumococcal pneumonia, thereby obliterating any apparent difference in severity between CAP caused by these 2 bacteria. Other investigators have shown that

Table 4. Outcomes in Patients With CAP due to *H. influenzae* Compared With CAP due to *S. pneumoniae*, With and Without Viral Coinfection[a]

	H. influenzae (n = 33)			*S. pneumoniae* (n = 36)			P Value for Comparison Between CAP Groups	
	No Viral Coinfection (n = 26)	Viral Coinfection (n = 7)	P Value	No Viral Coinfection (n = 27)	Viral Coinfection (n = 9)	P Value	SPn vs HI	SPnC vs HIC
Shock	0	0	—	14.8	11.1	.8	0.04	0.4
ICU admission	0	14.3	.05	14.8	22.2	.6	0.7	0.8
PORT score	100 [79–121]	85 [81–108]	.4	109 [86–137]	92 [82–100]	.3	0.2	0.7
Pneumonia Severity Index	4 [3–4]	3 [3–4]	.7	4 [3–5]	4 [3–4]	.7	0.2	0.4
ATS/IDSA severe pneumonia	5	1	.8	5	11.1	.6	1.0	0.8
qSOFA ≥2	11.5	28.6	.3	18.5	0	.2	0.02	0.2
In-hospital mortality	0	0	—	11.1	11.1	1.0	0.08	0.4
30-d mortality	0	0	—	14.8	11.1	.8	0.04	0.4

Abbreviations: ATS, American Thoracic Society; CAP, community-acquired pneumonia; HI, *Haemophilus influenzae* CAP with no coinfection; HIC, *Haemophilus influenzae* CAP with viral coinfection; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; PORT, Pneumonia Patient Outcomes Research Team; qSOFA, quick Sequential Organ Failure Assessment; SPn, *Streptococcus pneumoniae* CAP with no coinfection; SPnC, *Streptococcus pneumoniae* CAP with viral coinfection.

[a]Categorical variables are presented as percentage. Numeric variables are presented as median and interquartile range.

bacterial/viral coinfection causes severe CAP [26–28], but none has shown that the adverse effect of viral coinfection may vary greatly depending upon the bacterium.

We have recently shown that an etiologic diagnosis can readily be made in *Haemophilus* or pneumococcal pneumonia by examining gram-stained sputum and routine laboratory culture if a valid sputum sample is obtained at or soon after admission [4]. In that study, about 40% of *Haemophilus* isolates produced beta-lactamase, and none had been resistant to ampicillin/sulbactam, ceftriaxone, or fluoroquinolones.

A limitation of this study is that *Haemophilus* isolates were not typed. However, in 1983—even before the routine immunization of children with conjugate vaccine against *H. influenzae* type b (HIB)—we showed that cases of lower respiratory tract infection in adults were nearly all due to nontypeable isolates [1], and by now, *H. influenzae* type b has largely disappeared from the population in countries where HIB is routinely administered to the infants and toddlers. We cannot, however, exclude the possibility that some of our patients were infected with a typeable *Haemophilus.* A further limitation is that our study was limited to a single medical center with a great majority of middle-aged or older adults.

In conclusion, *Haemophilus influenzae* has become nearly equally as common a cause of pneumonia as *Streptococcus pneumoniae*. The same patient populations appear to be susceptible, but pneumonia caused by *Haemophilus* is less severe by many criteria, including the absence of altered mental status, extreme leukocytosis or leukopenia, bacteremia, septic shock, and death.

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