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Risk factors for the development of *Haemophilus influenzae* pneumonia in hospitalized adults

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ABSTRACT: Potential risk factors for developing *Haemophilus influenzae* nosocomial pneumonia have not been sufficiently studied. We wanted to investigate the incidence and risk factors for the development of *Haemophilus influenzae* pneumonia in the hospital by means of a multivariate analysis.

A total of 468 cases of nosocomial pneumonia were observed during the study period, 317 (68%) of which were aetiologically diagnosed by means of highly reliable methods, and *H. influenzae* was isolated in 57 of them. Fifty of the 57 episodes of *H. influenzae* pneumonia occurred in mechanically-ventilated patients. Underlying diseases were: medical in 12 cases, surgical in 15 cases, and traumatological in 22.

Variables associated with *Haemophilus influenzae* nosocomial pneumonia in intubated patients after the univariate analysis were: "period between admission and pneumonia 2–7 days" and "no previous antibiotics". A multivariate analysis demonstrated that the variables "no previous antibiotics" and "coma on admission" were risk factors for *H. influenzae* pneumonia. In nonintubated patients, no risk factors were found for *H. influenzae* pneumonia compared with other nosocomial pneumonia.

We conclude that *H. influenzae* was involved in 57 out of 317 (18%) of nosocomial pneumonia registered in our institution, and the majority of patients (50 out of 57) were mechanically-ventilated. In this particular subgroup, coma of the patient on admission to hospital and absence of antibiotic treatment prior to developing pneumonia constitute two definite risk factors for developing *H. influenzae* nosocomial pneumonia.

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Haemophilus influenzae (HI) frequently colonizes the trachea and major bronchi of smokers and patients with chronic obstructive pulmonary disease (COPD) [1]. *H. influenzae* infection is a common aetiology of exacerbations in COPD [2], and causes community-acquired pneumonia (CAP) in children and adults with chronic diseases, such as COPD or alcoholism [3, 4]. Nosocomial outbreaks of *H. influenzae* infection have recently been reported both in children and adults with chronic underlying disease [5].

During the last 15 yrs, several authors have reported descriptive studies on nosocomial *H. influenzae* infections [6–8], but the identification of potential risk factors for developing *Haemophilus influenzae* nosocomial pneumonia (HINP) by multivariate analysis has not previously been performed.

The aim of this study was to use univariate and multivariate statistical techniques to determine the risk factors for acquiring HINP.

Materials and methods

Study subjects

During a 6 year period (1984–1989), 468 patients who developed nosocomial pneumonia (NP) were prospectively evaluated. Our hospital is a 1,000 bed teaching hospital with a general intensive care unit (ICU) (36 beds), a cardiosurgery ICU (12 beds), and a neurosurgery ICU (5 beds). It is located in an urban area with a population of over 1.5 million and has an average admission of 25,000 patients·year^{-1}.

NP was defined as any new lung consolidation appearing 72 h after hospital admission, and at least two of the following conditions: 1) temperature >38°C; 2) leucocytosis >10,000 mm^3; 3) purulent secretions; and 4) blood gas abnormalities [9, 10]. Diagnosis of COPD was established using the standard criteria recommended by the American Thoracic Society [11]. Chronic

underlying diseases were considered according to the system described by McCABE and JACKSON [12]. Attributable mortality was defined when death occurred during antibiotic treatment without an alternative cause. Coma on admission was diagnosed when a score lower than nine was obtained using the Glasgow coma scale [13]. Prior antibiotic therapy was defined as having received any antimicrobial treatment during the period of hospital admittance.

Methods

Sputum or tracheal secretions were routinely Gram-stained [14] and cultured on general purpose media (blood agar, chocolate agar, and on differential medium McConkey agar). Quantitative cultures were not carried out. Two blood cultures were always collected. Pleural fluid examination and culture were carried out in the case of significant pleural effusion. In nonintubated patients, transthoracic needle aspiration (TNA) was performed according to the technique described by MANRESA and DORCA [15]. TNA samples were Gram-stained and inoculated into different media: blood agar, chocolate agar, McConkey agar, alpha-BCYE for Legionella in aerobic conditions, Brucella agar enriched with vitamin K and hemin in anaerobic conditions, and occasionally, into Lowenstein and Sabouraud media. In intubated patients, bronchoscopy with protected specimen brush (PSB) was carried out according to the technique of WIMBERLEY *et al*. [16]. PSB samples were quantitatively cultured in the previously specified media. A bacterial count $\geq 10^3$ colony forming units (cfu)·ml^{-1} was the cut-off point for diagnosing pulmonary infection, according to standard criteria [17]. Bacterial identification and susceptibility testing were carried out by standard methods [18]. HINP was diagnosed when *H. influenzae* was isolated from blood, pleural fluid, TNA or PSB. Non-HINP was defined when *H. influenzae* could not be cultured in these samples.

Analysis

Fifteen variables were considered: age, sex, period between admission and pneumonia, chronic underlying diseases, COPD, smoking, alcoholism, use of corticosteroids, a history of previous pneumonia, previous antibiotic treatment, the hospital-acquisition area, cranioencephalic trauma, coma on admission, duration of intubation, and surgery.

Proportions were compared using the chi-squared test with Yates correction or Fisher's exact test when necessary [19]. The odds ratios and their confidence intervals were calculated as described by SCHLESSELMAN [20]. A relative odds ratio for HINP of 1.0 was assigned to the lowest risk category for each variable. The multivariate analysis was performed using a step-forward logistic regression analysis as described by COX [21], with the level of significance equal to or lower than 0.05. All variables were entered into the regression analysis as categorical variables (0=absent or normal, 1=present or abnormal). All categorical variables which were not ordinal with two or more categories, such as hospital acquisition area, were defined as follows: 0=lowest risk category and the other categories were defined as 1, 2, 3, or 4, according to the level of significance obtained in the univariate analysis when compared with the lowest risk category. All calculations were performed using the SPSS software package and MULTR program ("Multiple Logistic Regression by Unconditional and Conditional Methods"; Ludwig Institute for Cancer Research-SP Branch).

Results

During the 6 year study period, a total of 468 episodes of nosocomial pneumonia were detected in our institution, 317 (68%) of which were aetiologically diagnosed by means of highly reliable methods. The aetiology of NP was Gram-negative bacilli (GNB) in 175 cases (55%), Gram-positive cocci (GPC) in 108 cases (34%), and *Legionella pneumophila* in 34 cases (11%). In the GNB group, *H. influenzae* was present in 57 cases (33%), 50 episodes occurring in intubated/ventilated patients. No epidemic outbreaks of HINP were detected during the study period. The chronic underlying diseases present in the HINP group were medical in 12 cases (21%), surgical in 15 cases (26%), and multiple trauma in 22 cases (39%) (including 10 patients with cranioencephalic trauma).

The aetiological diagnosis of HINP was obtained by means of: PSB in 53 cases (correlation with sputum culture in 40 cases); TNA in two cases (no correlation with

Table 1. – Clinical and microbiological data of HINP group

Patients n	57
Age yrs*	42±20
Sex M/F	44/13
Underlying disease	
No	8/57
Medical problems	12/57
Heart failure	8/12
COPD	2/12
Metabolic coma	1/12
Stroke	1/12
Surgical problems	15/57
Cardiac surgery	12/15
Abdominal surgery	3/15
Multiple trauma	22/57
Smoking	13/57
Days before pneumonia*	9.3±8.7
Intubation and mechanical ventilation	50/57
Previous antibiotics	21/57
Polymicrobial infection†	33/57
Staphylococcus aureus	20/33
Streptococcus pneumoniae	5/33
Gram-negative bacilli	3/33
Streptococcus agalactiae	2/33
Streptococcus sanguis	1/33
Corynebacterium equi	1/33
Bacteroides asaccharolyticus	1/33

*: mean±SD. †: in combination with *H. influenzae*; HINP: *H. influenzae* nosocomial pneumonia; M: male; F: female; COPD: chronic obstructive pulmonary disease.

sputum culture); and blood culture in two cases (correlation with sputum culture in one case). In two of the cases, the diagnosis of HINP was obtained by two different techniques (in one case by PSB and blood culture, and in another case by TNA and blood culture).

In 33 of the 57 HINP (58%), *H. influenzae* was isolated in combination with other organisms, but *H. influenzae* was predominant. The microbiological and clinical data of HINP cases are summarized in table 1. In the HINP group 18 out of 57 (32%) patients died. Mortality attributable to NP was observed in 5 out of 57 (9%) cases.

Table 2. – Risk factors for HINP in intubated patients, univariate analysis

Variables	HINP	non-HINP	Crude OR#	95% CI	p-value
Age					
>60 yrs	12	44	1.0		
20–60 yrs	28	101	1.1	0.4–6.8	NS
<20 yrs	10	15	2.4	0.8–6.8	NS
Sex					
Male	38	132	1.0		
Female	12	28	1.4	0.6–6.8	NS
Period between admission and pneumonia					
>14 days	9	60	1.0		
7–14 days	14	43	2.1	0.8–5.4	NS
2–7 days	27	57	3.1	1.3–7.2	0.007
Chronic underlying disease					
Yes	43	134	1.1	0.4–2.9	NS
No	7	26	1.0		
COPD					
Yes	5	18	1.0		
No	45	142	1.1	0.3–3.7	NS
Smoking					
Yes	11	33	1.1	0.5–2.3	NS
No	39	127	1.0		
Alcoholism					
Yes	2	12	1.0		
No	48	148	1.9	0.3–21	NS
Steroids					
Yes	5	26	1.0		
No	45	134	1.7	0.5–5.5	NS
Previous pneumonia					
Yes	1	20	1.0		
No	49	140	7	0.9–52	NS
Previous antibiotics					
Yes	19	116	1.0		
No	31	44	4.3	2–8.8	0.0001
Hospital acquisition area					
ICU	14	99	1.0		
Surgery	7	17	1.6	0.1–17	NS
Medicine	1	4	1.7	0.1–19	NS
CS-ICU	13	28	1.8	0.1–18	NS
NS-ICU	15	12	5	0.4–50	NS
Cranioencephalic trauma					
Yes	10	20	1.7	0.7–4	ns
No	40	140	1.0		
Coma on admission					
Yes	31	77	1.7	0.9–3.3	0.08
No	19	83	1.0		
Period of intubation					
>48 h	46	150	1.0		
<48 h	4	10	1.3	0.3–4.8	NS
Previous surgery					
Yes	21	62	1.1	0.6–2.1	NS
No	29	98	1.0		

ICU: intensive care unit; CS: cardiosurgery; NS: neurosurgery; #:OR: odds ratio; 95% CI: 95% confidence interval: NS: nonspecific. For further abbreviations see legend to table 1.

Table 3. – Risk factors for HINP in intubated patients, multivariate analysis

Variable	High risk category	Adjusted OR	95% CI	p-value
Previous antibiotics	Absent	4.3	3.1–6.6	0.001
Coma on admission	Present	2.5	1.1–5.8	0.2

Intubated and nonintubated patients were analysed separately. In the intubated group (table 2), the variables significantly associated with HINP in the univariate analysis were: "period between admission and pneumonia 2–7 days" ($p<0.007$) and "no previous antibiotics" ($p<0.0001$). All variables were introduced into a multivariate logistic regression model. After adjustment for confounding, only the variables "no previous antibiotics" ($p<0.001$) and "coma on admission" ($p<0.02$) were identified as significantly influencing the risk of developing HINP (table 3). In nonintubated patients, after the univariate and the multivariate analysis, no variables were identified as influencing the risk of HINP when compared with NP caused by other microorganisms.

Discussion

To investigate the incidence and associated risk factors for the development of HINP, we carried out a prospective study of 468 consecutive cases of NP seen in our institution during a period of 5 years; 317 of the cases could be aetiologically diagnosed by means of highly reliable methods. The incidence of HINP (alone or in combination with other pathogens) was 18% among the cases with a definite aetiological diagnosis. After a multivariate analysis, the conditions "coma on admission", and "no prior antibiotics" were found to be risk factors for the development of HINP.

One of the possible merits of our study, comparative to other series, is the fact that it is based on highly reliable aetiological diagnoses given by invasive methods, such as TNA and PSB [22].

Over the last several decades, cases of HINP have been described in patients with COPD, alcoholism, immunological deficiencies, sarcoidosis, and other conditions [6, 8, 23]. BARNES *et al.* [4] confirmed the association of *H. influenzae* community acquired pneumonia with chronic bronchitis, but did not establish its association with alcoholism or other conditions. This type of pneumonia was produced by microaspiration of oropharyngeal contents, and this mechanism has been confirmed in an experimental model [24].

Many clinical and epidemiological studies have demonstrated that the most frequent microorganisms causing NP are gram-negative bacilli (GNB) [9]. Nonepidemic HINP is uncommon in clinical practice, and its incidence

varies, depending on the particular series analysed. In a study of nosocomial respiratory infection in surgical patients, KINNER *et al*. [25] found that *H. influenzae* was the second most common cause of respiratory infection. BARTLETT *et al*. [23], in a study which involved 159 NP patients diagnosed mainly by transtracheal needle aspiration, found an incidence of 17%; but this technique can produce up to 40% false positives in patients with chronic respiratory pathology, due to the common colonization of their bronchial tree by organisms such as *H. influenzae* [25, 26].

In intubated patients, the incidence of HINP has not been clearly established, varying between 1–35% [17, 27]. Risk factors for some aetiologies of NP such as *Staphylacoccus aureus*, have been studied previously [28], but not in the case of *H. influenzae*.

SIMON *et al*. [6] correlated the results of 100 *H. influenzae* sputum cultures with the clinical and radiological criteria of respiratory infection in a hospital population, and they found that 35 out of 100 cultures were related to a real respiratory infection (25 pneumonia and 10 bronchitis), and 65 out of 100 to colonization of the airway. In 10 out of the 35 (29%) patients with respiratory infection, *H. influenzae* was acquired in hospital, and in this group 14 out of 35 (40%) of the patients had COPD and 16 out of 35 (46%) were intubated. They concluded that COPD and intubation were the predisposing factors for *H. influenzae* nosocomial infection.

MILLER and CAPLAN [7] described the incidence and risk factors for HINP in a group of mechanically-ventilated patients. The diagnosis of pneumonia was established on the basis of clinical and radiological criteria and a positive tracheal aspirate culture. All patients with HINP were intubated, had suffered multiple trauma, and were in hospital for a short period of time before the onset of pneumonia. Because of the young age of the study population and the fact that pneumonia developed shortly after admission, MILLER and CAPLAN [7] concluded that these patients had been colonized prior to admission. The pneumonia acquisition mechanism was aspiration of oropharyngeal content. In the same way, DILWORTH *et al*. [29] have described a particular clinical picture in postoperative patients, usually known as "early pneumonia", which is formally a nosocomial infection caused by the patient's own pharyngeal flora. Our study supports the pathogenic mechanism of the aspiration of the patient's own flora.

Recently, RELLO *et al*. [8] described the incidence and risk factors of HINP in intubated patients. These authors established the diagnosis of HINP on the basis of results obtained by PSB. The majority of patients had head trauma and surgery as underlying diseases. They studied 13 risk factors and, after univariate analysis, only the absence of previous antibiotics was considered a risk factor.

According to the data afforded by the literature, a multivariate analysis should be performed in order to identify variables independently influencing the risk of HINP. Our study was designed to determine which risk factors were associated with the development of HINP compared with NP caused by other microorganisms, and this analysis is useful in clinical practice. Nevertheless, if we want to evaluate the factors which influence the development of HINP in a general population of adult patients, a case-control study is necessary.

The results of our univariate analysis partially coincided with the findings of MILLER and CAPLAN [7], SIMON *et al*. [6] and RELLO *et al*. [8]. HINP was observed early in the hospital stay, in both young and intubated patients, and in patients without prior antimicrobial therapy. The populations studied by MILLER and CAPLAN [7] and SIMON *et al*. were different from those analysed in this study, but the population studied by RELLO *et al*. also included patients admitted to a general ICU. Our study included patients admitted to different hospital areas. The diagnostic methods used to confirm the presence of pneumonia were also different: in the present study the highly reliable TNA and PSB methods were used. The study of MILLER and CAPLAN [7] is descriptive and that of SIMON *et al*. [6] is retrospective.

In the multivariate analysis, the variables "no previous antibiotics " and "coma on admission" were identified as risk factors of HINP in mechanically-ventilated patients. In the nonintubated group, we did not find any risk factor associated with HINP compared with NP produced by other microorganisms. These last results should be interpreted cautiously, due to the small number of nonventilated HINP.

H. influenzae is reported to be isolated in combination with *S. aureus* [30]. Coma has been a recognized risk factor of *S. aureus* nosocomial pneumonia in intubated patients [28]. In our study, *S. aureus* was isolated in combination with *H. influenzae* in 11 out of 31 (35%) intubated patients with coma on admission. Nevertheless, *H. influenzae* was the sole microorganism in 20 out of 31 (65%) NP in this specific population. The high specificity of the diagnostic techniques used in this study strongly supports the diagnosis of mixed pneumonia. *H. influenzae* is frequently isolated from the upper respiratory tract secretions of normal individuals. Probably, coma facilitates the aspiration of oropharyngeal content, and consequently the development of NP caused by organisms such as *H. influenzae* or *S. aureus*.

Intubated patients with coma on admission and without prior antibiotics present a definite risk factor for having HINP. Most antibiotics normally prescribed on an empirical basis for different infections in this setting are active against *H. influenzae*, therefore preventing the development of *H. influenzae* respiratory infection in favour of more resistant organisms. This fact must be taken into account before empirical antibiotic prescription. Probably a "selective" regimen, mainly covering organisms such as *H. influenzae* or *S. aureus* (*e.g.* second generation cephalosporins or amoxicillin-clavulanate), are preferable, to the systematic prescription of broad spectrum antibiotics. These predispose to superinfection by multiresistant Gram-negative bacilli, associated with higher morbidity and mortality.

References

1. Smith CB, Golden CA, Kanner RE, Renzetti AD. *Haemophilus influenzae* and *Haemophilus parainfluenzae* in

chronic obstructive pulmonary disease. *Lancet* 1976; i: 1253–1255.
2. Mc Hardy VU, Inglis JM, Calder MA, Crofton JW, Gregg I, Ryland DA. A study of infective and other factors in exacerbations of chronic bronchitis. *Br J Dis Chest* 1980; 74: 228–238.
3. Woodhead MA, McFarlane JT. *Haemophilus influenzae* pneumonia in previously fit adults. *Eur J Respir Dis* 1987; 70: 218–220.
4. Barnes D, Naraoi S, Igo J. *Haemophilus influenzae* in Melanesian adults: report of 15 cases. *Thorax* 1987; 42: 889–891.
5. Sturm AW, Mostert R, Roning PJ, Klingeren BV, Alphenj L. Outbreak of multiresistant nonencapsulated *Haemophilus influenzae* infections in a pulmonary rehabilitation center. *Lancet* 1990; 335: 214–216.
6. Simon HB, Southwick FS, Moellering RC, Sherman E. *Haemophilus influenzae* in hospitalized adults: current perspectives. *Am J Med* 1980; 69: 219–226.
7. Miller EH, Caplan ES. Nosocomial *Haemophilus influenzae* in patients with severe trauma. *Surg Gyn Obst* 1984; 159: 153–156.
8. Rello J, Ricart M, Ausina V, Net A, Prats G. Pneumonia due to *Haemophilus influenzae* among mechanically-ventilated patients: incidence, outcome and risk factors. *Chest* 1992; 102: 1562–1565.
9. Fagon J, Chastre J, Domart Y, *et al*.. Nosocomial pneumonia in patients receiving continuous mechanical-ventilation: analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. *Am Rev Respir Dis* 1989; 139: 877–884.
10. Centers for Disease Control. National Nosocomial Infections Study Site Definitions Manual. Atlanta, Centers for Disease Control, 1972, pp. 82–84.
11. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987; 136: 225–244.
12. McCabe WR, Jackson GG. Gram-negative bacteriemia: clinical, laboratory and therapeutic observations. *Arch Intern Med* 1962; 110: 856–864.
13. Rimel RW, Tyson GW. The neurologic examination in patients with central nervous system trauma. *J Neurosurg Nurs* 1979; 12: 148–152.
14. Murray PR, Washington JA. Microscopic and bacteriologic analysis of expectorated sputum. *Mayo Clin Proc* 1975; 50: 339–344.
15. Manresa F, Dorca J. Needle aspiration techniques in the diagnosis of pneumonia. *Thorax* 1991; 46: 601–603.
16. Wimberley NW, Bass JB, Boyd BW, Kirkpatrick MB, Serio RA, Pollock HM. Use of bronchoscopic protected catheter brush for the diagnosis of pulmonary infections. *Chest* 1982; 81: 556–562.
17. Chastre J, Vian F, Brun F, Pierre J, Dange MC, Bouchame A. Prospective evaluation of the protected specimen brush for the diagnosis of pulmonary infections in ventilated patients. *Am Rev Respir Dis* 1984; 130: 924–929.
18. Lennette ET, Bullows A, Hansler WJ, Shadomy HJ. Manual of Clinical Microbiology. Washington, DC, American Society for Microbiology, 1985; pp. 160–200.
19. Armitage P. Statistical Methods in Medical Research. Oxford, Blackwell Scientific, 1971; p. 504.
20. Schlesselman JJ. Case Control Studies: Design, Conduct, Analysis. New York, Oxford University press, 1982; pp. 220–230.
21. Cox DR. The analysis of binary data. London, Chapman and Hall, 1970; p. 142.
22. Dorca J, Manresa F, Esteban Ll, *et al*. Efficacy, safety and therapeutical relevance of transthoracic needle aspiration with ultra-thin needle in nonventilated nosocomial pneumonia. *Am J Respir Crit Care* Med 1995; 151: 1491–1496.
23. Barlett JG, O'keefe P, Tally FP, Louise TJ, Gorbach SL. Bacteriology of hospital-acquired pneumonia. *Arch Intern Med* 1986; 146: 868–871.
24. Exposito AL, Pennington JE. Experimental pneumonia due to *Haemophilus influenzae*: observations on pathogenesis and treatment. *J Infect Dis* 1984; 149: 728–734.
25. Kinner WJM, Finch RG, Pilkington R, MacFarlane JT. Nosocomial lower respiratory tract infections in surgical wards. *Thorax* 1990; 45: 187–189.
26. Bjerkestrand G, Digranes A, Schreiner A. Bacteriological findings in transtracheal aspirates from patients with chronic bronchitis and bronchiectasis. *Scand J Respir Dis* 1975: 56: 201–207.
27. Rello J, Quintana E, Ausina V, Castella J, Luquin M, Net A. Incidence, etiology and outcome of nosocomial pneumonia in mechanically-ventilated patients. *Chest* 1991; 100: 439–444.
28. Rello J, Quintana E, Ausina V, Puzo C, Net A, Prats G. Risk factors for *Staphylococcus aureus* nosocomial pneumonia in critically ill patients. *Am Rev Respir Dis* 1990; 142: 1320–1324.
29. Dilworth JP, White RJ, Brown EM. Microbiol flora of the trachea during intubation of patients undergoing abdominal surgery. *Thorax* 1992; 47: 818–820.
30. Espersen F, Gabrielsen J. Pneumonia due to to *Staphylococcus aureus* during mechanical ventilation. *J Infect Dis* 1981; 144: 19–23.