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Bacterial Etiology of Chronic Bronchitis Exacerbations Treated by Primary Care Physicians

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OBJECTIVE: Few studies have been carried out to determine the prevalence of microorganisms causing exacerbations of chronic bronchitis in the community setting. The aim of the present study was to determine the bacterial etiology of chronic bronchitis exacerbations in patients not requiring hospitalization.

PATIENTS AND METHODS: This observational, cross-sectional, multicenter study was carried out at the primary care level during 2 weeks (in November 2001 and January 2002). All laboratory work was carried out at a single center. We studied 1947 patients with mild-moderate exacerbations treated by 650 primary care physicians. All the sputum samples received for centralized processing were subject to Gram staining, microscopic examination, and bacterial culture.

RESULTS: Out of 1537 cultures of sputum samples collected, 498 had good cell quality for microscopic examination (32.4%). Of the 498 good quality samples analyzed, 246 (49.4%) were positive and 468 isolates were obtained. The most commonly isolated germ was *Streptococcus pneumoniae* (163 cases, 34.8%), followed by *Moraxella catarrhalis* (112, 23.9%), and *Haemophilus influenzae* (59, 12.6%). In 1.2% of the *S pneumoniae* isolates resistance was found to amoxicillin; resistance to macrolides was found in 34.3%. The antibiotics most commonly prescribed, however, were macrolides (38.3% of the prescriptions).

CONCLUSIONS: *S pneumoniae* was the microorganism most frequently isolated in cases of chronic bronchitis exacerbation treatable in this outpatient setting.

Key words: *Bronchitis, chronic. Acute exacerbation. Etiology.*

Etiología bacteriana de la agudización de la bronquitis crónica en atención primaria

OBJETIVO: Pocos estudios se han efectuado en el ámbito comunitario para conocer la prevalencia de microorganismos causantes de agudizaciones de la bronquitis crónica. El objetivo del presente estudio ha sido conocer la etiología bacteriana de la agudización de la bronquitis crónica en pacientes que no han requerido hospitalización.

PACIENTES Y MÉTODOS: Se trata de un estudio observacional, transversal y multicéntrico, efectuado en atención primaria de salud durante 2 semanas (noviembre de 2001 y enero de 2002) con un laboratorio central. Participaron 1.947 pacientes afectados de agudización leve-moderada incluidos por un total de 650 médicos de atención primaria. Todas las muestras recibidas se procesaron en un laboratorio central con tinción de Gram, examen microscópico de las muestras y cultivo bacteriano.

RESULTADOS: Entre los 1.537 cultivos de esputo recogidos, 498 presentaron buena calidad celular microscópica (32,4%). De las 498 muestras de esputo de calidad óptima analizadas, fueron positivas 246 (49,4%) y se obtuvieron 468 aislamientos. El germen más comúnmente aislado fue *Streptococcus pneumoniae*, con 163 casos (34,8%), seguido de *Moraxella catarrhalis*, con 112 (23,9%), y *Haemophilus influenzae*, con 59 (12,6%). El 1,2% de los neumococos fueron resistentes a amoxicilina y un 34,3% a los macrólidos. Los antibióticos mayormente prescritos fueron, sin embargo, los macrólidos, en el 38,3% de las ocasiones.

CONCLUSIONES: *S. pneumoniae* constituye el microorganismo bacteriano que con más frecuencia se aísla de los pacientes que sufren agudizaciones de la bronquitis crónica que pueden ser tratados ambulatoriamente.

Palabras clave: *Bronquitis crónica. Agudización. Etiología.*

Introduction

Chronic obstructive pulmonary disease (COPD) and chronic bronchitis are major causes of morbidity in developed countries and count among the principal causes of death worldwide.[1] Exacerbations of chronic bronchitis also have considerable impact on health care system at both the primary and tertiary care levels, as they are a major reason for antibiotic use and admissions; additionally, exacerbations lead to indirect

This study received funding from Sanofi-Aventis.

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Manuscript received June 22, 2005. Accepted for publication December 13, 2005.

costs because of days lost from work.[2] The role of bacterial infection in exacerbations of chronic bronchitis and the use of sputum cultures to reach an etiological diagnosis to guide clinical management in this setting are subjects of current debate.[3] *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis* account for over half the bacteria isolated in respiratory samples from patients with exacerbated chronic bronchitis and the figure may even reach 75%.[4] Other pathogens, such as respiratory viruses and atypical bacteria, have also been implicated.[5-8] The contributions of these organisms can be seen to vary from series to series, largely in function of the severity of the underlying obstructive disease.[9]

Over 90% of patients with exacerbated chronic bronchitis are treated with antibiotics,[10] although the effectiveness of many is uncertain because of the emergence of resistant strains of the most common respiratory pathogens in the past 15 years. The rate of resistance of *S pneumoniae* to some antibiotics, mainly empirically prescribed drugs, has increased, and though macrolides continue to be prescribed for respiratory infections, the rates of resistance to them is now high.[11,12]

The main purpose of this study was to determine the prevalence of the most common respiratory pathogens in patients with exacerbated chronic bronchitis treated as outpatients. We also sought to identify the rates of resistance to the antibiotics most commonly used in primary care and to analyze physician prescribing patterns.

Patients and Methods

An observational study of patients with exacerbated chronic bronchitis was carried out for 1 week in November 2001 and 1 week in January 2002; 650 primary care physicians from all over peninsular Spain (not including the Canary or Balearic Islands, or the cities of Ceuta or Melilla) participated. The participating physicians each had to recruit 3 consecutive patients with symptomatic chronic bronchitis. Recruited patients were to have a history of chronic cough and sputum production lasting 3 months for 2 consecutive years according to the criteria of the American Thoracic Society.[13] They were also to present an exacerbation, defined by increased dyspnea, evident increase of respiratory secretions and/or a change in sputum characteristics, and at least 1 of the following 3 criteria: increased cough frequency, increased cough severity, and/or fever (>37°C). Patients were excluded if they had received an antibiotic in the last 30 days; if they had suspected pneumonia, asthma, or cystic fibrosis; or if they had bronchiectasis as a sequela of tuberculosis or any other disease process.

Data collected were age, sex, smoking history, and the prescribed antibiotic. A sputum sample was collected from each patient and refrigerated until sent to the central laboratory (Instituto Valenciano de Microbiología) within 12 hours. Transport was by messenger and the sample was kept refrigerated. The appearance of each sputum sample was assessed and then it was washed twice in physiologic saline solution. Aliquots for Gram staining and culture were taken and the rest of the sample was divided in half and frozen at –20°C. Sputum sample quality was evaluated by checking the number of inflammatory and epithelial cells; samples were considered viable if there were at least 10 epithelial cells and more than 25 polymorphonuclear leukocytes per high power field, in accordance with the criteria of Murray and Washington[14] and Heineman et al.[15] Bacterial isolates were identified with conventional microbiologic methods.

To determine antibiotic sensitivity, microdilution tests were performed to establish the minimum inhibitory concentration (MIC) of each drug. The double disk method was used to determine the phenotype of resistance of *S pneumoniae* to macrolides. Also performed were tests to detect β-lactamase in *H influenzae* and *M catarrhalis* and the macrolide resistance genes in *S pneumoniae*. The MIC microdilution tests were performed for penicillin, amoxicillin, clavulanic acid, acetyl cefuroxime, erythromycin, clarithromycin, azithromycin, ciprofloxacin, and levofloxacin following the instructions of the National Committee for Clinical Laboratory Standards of 2001 and for telithromycin following the instructions for 2003.

Descriptive statistics were compiled for the results.

Results

The 650 primary care physicians recruited 1947 patients. As sputum samples could not be collected from 410, a total of 1537 samples were processed by the Instituto Valenciano de Microbiología (78.9%) (Figure). The mean (SD) age of the 1537 patients participating was 60.3 (16.6) years; 67.7% were men and 31.4% were current smokers. Viability was checked microscopically and cellular quality was good in 498 samples (32.4%). The 1039 remaining samples (67.6%)

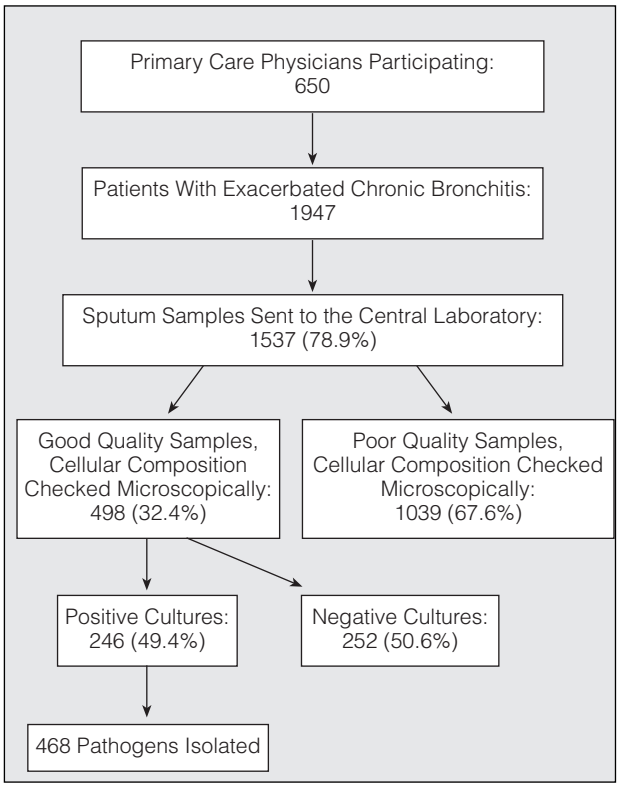

Figure. Diagram showing the structure of the study.

TABLE 1
Pathogens Isolated From Sputum Cultures (n=468)*

Pathogen	No (%)
Streptococcus pneumoniae	163 (34.8)
Moraxella catarrhalis	112 (23.9)
Haemophilus influenzae	59 (12.6)
Escherichia coli	27 (5.7)
Staphylococcus aureus	25 (5.3)
Pseudomonas aeruginosa	23 (4.9)
Streptococcus pyogenes	21 (4.4)
Klebsiella pneumoniae	12 (2.5)
Nonfermenting Gram-negative bacilli	8 (1.7)
Proteus species	6 (1.2)
Enterobacter species	6 (1.2)
Haemophilus parainfluenzae	3 (0.6)
Serratia species	1 (0.2)
Providencia species	1 (0.2)
Total	468

*Potentially pathogenic bacterial isolates (1 or more) were found in 246 sputum cultures.

were not used for microbiology, even though microorganisms were detected in 222 (21.4%) of them; *S pneumoniae* and *M catarrhalis* were the most frequent isolates in those samples, at 38% and 20%, respectively. They were not computed among causative agents, however, but rather excluded from sensitivity studies. Of the 498 sputum samples of optimal quality analyzed, normal flora was isolated in 252 and 1 or more respiratory pathogens in 246 (49.4%). In 168 (67.5%) a single pathogen was isolated whereas 2 or more were isolated in the remaining samples. Of the total number of isolates (n=468), the most commonly identified pathogens were *S pneumoniae* (34.8%), *M catarrhalis* (23.9%), and *H influenzae* (12.6%) (Table 1).

Resistance to penicillin was found in 47.2% of the *S pneumoniae* isolates, though resistance was high in only 2.6%. In contrast, the rate of resistance to amoxicillin was 1.2%. Macrolide resistance was detected in 34.3% of the *S pneumoniae* isolates, with no distinction between erythromycin, clarithromycin, and azithromycin (Table II). A constitutive phenotype was demonstrated for 87.5% of the resistant *S pneumoniae* strains, and an M phenotype for 12.5%; inducible resistance was not observed for any isolate. Levofloxacin resistance was detected in 4.2% of the *S pneumoniae* strains, at a MIC of 8 µg/mL or more; all of them were sensitive to penicillin and amoxicillin. β-lactamase producing *H influenzae* or *M catarrhalis* were found in 25.5% and 82% of the isolates, respectively. No *H influenzae* or *M catarrhalis* isolates were found to be resistant to amoxicillin or clavulanic acid. The antibiotic treatment prescribed was not recorded for 3 cases. Some form of antibiotic treatment was prescribed for 1342 (99.1%) and none was prescribed for 12. Macrolides were the antibiotics most often prescribed, in 518 exacerbations (38.3%), followed by the combination of amoxicillin and clavulanic acid in 401 (29.6%) (Table 3).

Discussion

Before discussing the results of this study it is important to consider its limitations. This multicenter study involving primary care clinics in peninsular Spain enrolled patients with a clinical diagnosis of chronic bronchitis, not patients with COPD, given that spirometry was not performed. It is important to remember that not all patients with chronic bronchitis have airflow obstruction and exacerbations tend to be less severe in the absence of such flow limitation. Another study limitation is related to the definition of exacerbation. Individuals with chronic bronchitis symptoms were included only if they had a concomitant increase of dyspnea and either increased sputum production or a change in sputum color. Then, they also had to meet 1 of 3 additional criteria: increased cough frequency, more severe cough, or fever. Thus, all the recruited patients had 2 or more of the criteria established by Anthonisen et al[16] for antibiotic treatment, and it should not be surprising that 99.1% received prescriptions. They were required to have either fever or worse cough, and although the percentages for each sign are not available, it is logical to assume that most of these patients were coughing more. Nevertheless, while the physicians were asked to exclude patients suspected of pneumonia, it was

TABLE 2
Prevalence of Resistance of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* to Various Antibiotics*

Antibiotics	*S pneumoniae*	*H influenzae*		*M catarrhalis*	
		BL +	BL –	BL –	BL –
Penicillin	47.2†	NC	NC	NC	NC
Amoxicillin	1.2	NC	NC	NC	NC
Amoxicillin + clavulanic acid	1.2	0	0	0	0
Acetyl cefuroxime	13.6	0	0	0	0
Erythromycin	34.3	NC	NC	NC	NC
Clarithromycin	33.1	0.6	0.6	0	0
Azithromycin	33.1	0	0	0	0
Telithromycin	0	0	0	0	0
Levofloxacin	4.2	0	0	0	0
Ciprofloxacin	NC	0	0	0	0

*BL indicates β-lactamase; NC, no criteria are available from the National Committee for Clinical Laboratory Standards, 2001, regarding cutoff points for sensitivity versus resistance.
†Intermediate resistance, 0.12-1 µg/mL: 44.6%; high resistance, ≥2µg/mL: 2.6%.

TABLE 3
Empirically Prescribed Antibiotic Treatment*

Antibiotics	No. (%)
Macrolides	518 (38.3)
Amoxicillin + clavulanic acid	401 (29.6)
Fluoroquinolones	228 (16.8)
Oral cephalosporins	140 (10.3)
Amoxicillin	33 (2.4)
Other antibiotics†	22 (1.7)
No antibiotics	12 (0.9)
Total	1354

*Includes parenteral cephalosporins, tetracyclines, both macrolides and β-lactam antibiotics, and both macrolides and fluoroquinolones.

possible for them to enroll patients with fever, so it can not be guaranteed that no one with pneumonia entered the study. Still, because of the definition of fever in this study (presence of an axillary temperature >37°C) and the fact that physicians were instructed to exclude doubtful cases, the possibility that patients with pneumonia were recruited is frankly remote. This is important because the pathogen most often isolated in this study was *S pneumoniae*. Furthermore, high fever in exacerbated chronic bronchitis, once pneumonia has been ruled out, is usually due to viral infection.[17]

Another limitation is the poor yield of the samples sent to the laboratory. A total of 410 patients had to be dropped because no sample had been collected; therefore analyses were made based on samples from 1537. The fact that the study was carried out from primary care clinics may explain why only 32.4% of the samples sent had the features characteristic of lower airway specimens whereas the 67.6% remaining ones appeared to be mucous contaminated by saliva. This low percentage of viability for microbiology is unsurprising given that sputum samples are not usually cultured in ambulatory settings except in very concrete circumstances. Viability is naturally greater in a hospital setting, given that staff are trained for and experienced with sample collection. Nevertheless, nearly half the sputum samples sent by the primary care doctors that met the internationally established quality criteria were positive, as has been the case in other studies.[6,18,19] Curiously, 2 or more germs were isolated in approximately a third of the positive cultures in our study. This rate is slightly higher than that reported in other studies,[8,9,20] although it is similar to the pattern seen by Soler et al[21] in severely ill hospitalized patients. Studies in recent years have shown an association between exacerbation and an increased number of bacterial colony forming units,[6,21] the acquisition of new bacterial strains,[22] and increased bronchial inflammation caused by bacteria,[23] supporting the hypothesis of a bacterial etiology for some or most cases of exacerbated chronic bronchitis. Studies that have analyzed the microbiology of chronic bronchitis exacerbation in detail have implicated 1 or more bacteria in over half the episodes.[24] Sophisticated, invasive diagnostic techniques such as endoscopic protected brush sampling of the tracheobronchial tree by endoscopy can facilitate the isolation of potentially pathogenic bacteria in around 65% of exacerbations.6 Considering that between 29% and 35% of these patients are chronically colonized when stable,[6,25] it is reasonable to assume that new bacteria are identified in 30% to 35% of exacerbations. Moreover, the residual bacterial colonization after antibiotic treatment of an exacerbation influences the rate and severity of later exacerbations.[26]

In our study, the bacteria that were isolated most often were *S pneumoniae, M catarrhalis*, and *H influenzae*, in that order. Those 3 bacteria together accounted for 71.3% of the isolates. *S pneumoniae* was the most frequently isolated, unlike other studies in which *H influenzae* was the most common pathogen.[3,6,25,27] Viejo et al[28] observed a 39% prevalence of *Haemophilus* species in a study of several hospitals in a northern area of Spain. The difference between their findings and ours may be attributable to the lower degree of severity of respiratory disease in our patient population, as all had exacerbated chronic bronchitis treatable on an outpatient basis. The prevalence of pathogen isolation is greater among patients with a more severe stage of lung disease and among those who continue smoking. Eller et al[8] isolated more enterobacteria and *Pseudomonas aeruginosa* in severe COPD exacerbations and more *H influenzae* in less seriously ill patients. In other studies, gram-negative bacilli such as *Escherichia coli, Proteus mirabilis, Serratia marcescens*, and *P aeruginosa* have been identified in sputum or bronchoscopic samples in exacerbations that required mechanical ventilation or in advanced disease in which forced expiratory volume in 1 second (FEV_1) was less than 50% of predicted.[21] In a study of 40 patients with stable COPD of varying degrees of severity, the prevalence of gram-negative bacilli colonizing the oropharynx increased with severity of underlying respiratory alteration; a prevalence of 0% was found in mild disease, 7.7% in patients with moderate disease, and 29.4% in patients with FEV_1 less than 50% of predicted.[29] Zalacaín et al[30] observed that 40% of their 88 patients with stable COPD and an average FEV_1 of 55% of predicted were colonized and that the germ isolated most often was *H influenzae*. Moreover, they found that severe bronchial obstruction carried a relative risk of colonization of 5.1 in comparison with mild obstruction. Along the same lines, Monsó et al[31] found colonization in only 22% of their patients, probably because they studied a population with milder disease, indicated by an average FEV_1 of 74% of predicted. Perhaps the best indication of this trend in Spain came from a study by Miravitlles et al,[9] who found that risk of exacerbation caused by *H influenzae* or *P aeruginosa* was 6 times greater for COPD patients with severe disease than for those whose FEV_1 was greater than 50% of predicted. In that study, as in ours, both *S pneumoniae* and *M catarrhalis* were more prevalent than *H influenzae* among patients with FEV_1 greater than 50%. Also similar to our findings were those of Eller et al,[8] who recorded more *S pneumoniae* than *Haemophilus* species isolates for patients with exacerbations of mild-moderate COPD.

The rates of resistance we observed revealed the very interesting finding of amoxicillin activity against *S pneumoniae*, whose rate of resistance was 1.2%—a figure that was considerably lower than the rates reported from other Spanish studies.[11,12] Similarly, the prevalence of strains that were highly resistant to penicillin was very low in our study. In contrast, we observed high rates of resistance of *S pneumoniae* to several antibiotics, with the exception of penicillin; specifically, resistance was detected to macrolides, with no distinctions among erythromycin, clarithromycin, and azithromycin. A worrying finding, however, was the 4.2% rate of *S pneumoniae* strains resistant to levofloxacin. This finding would confirm a trend in Spain toward increased rates of resistance to the so-called respiratory fluoroquinolones in *S pneumoniae* strains.

Although we did not evaluate the clinical and bacteriologic effectiveness of the empirically prescribed antibiotic therapy—and this would count as another study limitation—we consider it important to analyze the appropriateness of the patterns observed in relation to the rates of *S pneumoniae* resistance to the various antibiotics. While atypical pathogens and viruses can also be implicated in exacerbations of chronic bronchitis,[32] antibiotic treatment should be prescribed based on the 3 most commonly found microorganisms (*M catarrhalis, H influenzae*, and *S pneumoniae*) and particularly considering the resistance to macrolides of *S pneumoniae* strains. In this sense, the 38.3% rate of macrolide prescription can be considered too high; cost increases related to risk of treatment failure have also been linked to these antibiotics.[33] In contrast, less than 30% of cases were treated with the combination of amoxicillin and clavulanic acid, the antibiotic regimen of choice according to current guidelines.[34-37] Another finding for concern regarding therapy was that nearly 17% of the patients were treated with fluoroquinolones. That figure seems too high to us considering that their chronic bronchitis exacerbations were mild or moderate.

In summary, it is important for the primary care physician to be aware of the most common etiologies of chronic bronchitis or COPD exacerbations in the community and the rates of resistant pathogens isolated in outpatients in order to choose which antibiotic to prescribe. The antibiotic chosen should necessarily cover the greatest number of *S pneumoniae* strains, and this means that macrolides—to which 35% of these strains are currently resistant—should not be recommended.

Acknowledgments

We thank all the primary care physicians who participated in this study. We gratefully acknowledge the work of Juan García-de-Lomas, Encarnación Esteban, and Concepción Gimeno of the Instituto Valenciano de Microbiología in Valencia for the microbiological studies. We also thank Aventis Pharma for financing the logistics for this study.

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