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Prognosis of COPD patients requiring frequent hospitalization: Role of airway infection

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Summary
Rationale: A subgroup of patients with chronic obstructive pulmonary disease require frequent hospitalization because of exacerbations of the disease. We hypothesized that airway infection by non-usual pathogens is a major factor driving hospitalization needs in these patients.
Objectives: 1) To describe the clinical and functional characteristics of a cohort of COPD patients requiring ≥2 hospitalizations per year; 2) to determine prospectively their microbiological pattern during exacerbations; and, 3) to analyze the prognostic value of several clinical, functional and microbiological variables with respect to hospitalizations and mortality.
Methods: Open cohort study of 116 COPD patients who had been hospitalized at least twice during the last 12 months. Patients were followed for an average of 21 months.
Measurements and main results: Clinical data, forced spirometry and 6 min walking distance were determined, and the BODE index was calculated, at the time of inclusion in the study. During follow-up, sputum culture was obtained during exacerbations, and hospitalization and mortality were collected every two months. Mean age was 71 yrs, and 94% of patients were male. Main findings show that: 1) not all patients had severe disease according to either the degree of airflow limitation or the BODE index; 2) non-usual pathogens, mainly *Pseudomonas aeruginosa*, other gram-negative non-fermentative rods and Enterobacteriaceae, were isolated among 71.1% of the sputum obtained during exacerbations; and, 3) these pathogens were associated with poor prognosis and frequent hospitalization.

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Conclusions: Airway infection by non-usual pathogens appears to be a key driver of frequent hospitalizations and mortality in COPD.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) often present with episodes of exacerbation (ECOPD) during the course of their disease. These episodes are important events in the natural history of COPD because they accelerate the decline of lung function, worsen the prognosis of the patient[1,2] and impose a significant economic burden on society.[3–5]

Although the mechanisms of ECOPD are likely to be multi-factorial, it is widely accepted that airway bacterial infection plays a key pathogenic role.[6] Besides, chronic airway colonization is recognized today as an important driver of COPD progression.[7] Not all COPD patients, however, have airway bacterial colonization, and the frequency of ECOPD also varies greatly among them. Thus, whereas some patients never present ECOPD, others exacerbate several times every year. Among the latter, there is a subgroup of patients who are hospitalized repeatedly.[8] The clinical, functional and microbiological characteristics of these patients are poorly understood. We hypothesized that airway infection by non-usual pathogens is a major factor driving hospitalization requirements in these latter subgroup of COPD patients.

In 2002, we instituted in our hospital an integrated, multidisciplinary program aimed at providing clinical, rehabilitation and educational support to patients with advanced COPD (Online supplement Table E1), like others have done before successfully.[9–12] Therapeutic strategies were established by severity levels in stable COPD, and aiming to identify and manage ECOPD, according to GOLD guidelines.[13] Because one of the possible criteria for inclusion in our program was that the patient had required hospitalization because of ECOPD two or more times during the last 12 months, this program offered us the opportunity to characterize and follow-up this particular sub-population of COPD patients. Accordingly, in this study we aimed: (1) to describe their clinical and functional characteristics at the time of inclusion in our program; (2) to determine prospectively the microbiological pattern of airway infection during ECOPD; and, (3) to analyze the prognostic value of several clinical, functional and microbiological variables with respect to the frequency of hospitalizations and mortality.

Methods

Patients

From October 2002 to December 2006, we included in our program, after obtained informed consent, 202 patients with advanced respiratory disease, of whom 140 required two or more respiratory hospitalizations during the last 12 months. Of these, 116 were diagnosed of COPD according to the GOLD guidelines.[13] All patients with diagnoses other than COPD were excluded of our study (Fig. 1).

Design of the study

This is an open cohort observational study. At the time of inclusion in our program, clinical data were obtained in stable phase (that is at least one month after the last ECOPD). Spirometry was obtained in all subjects and in 107 of them, the 6 min walking distance (6MWD) was also determined. Patients were then followed-up during an average of 21 months (range, 1—51 months). During this period, patients were visited every two months, or more often if clinically required or by patient request. The study protocol was approved by our Hospital Research Committee.

Measurements

Dyspnea was quantified using the modified Medical Research Council (mMRC) questionnaire.[14] Co-morbidities were assessed using the Charlson index.[15] Spirometry was measured according to standard international recommendations.[16] Reference values correspond to a Mediterranean population.[17] The 6-min walking distance (6MWD) was determined following 2002 ATS guidelines.[18] The BODE index was calculated according to Celli et al.[19]

Culture of spontaneous sputum was obtained in all ECOPD episodes that fulfilled GOLD criteria,[13] occurred during follow-up and, according to the criteria of Anthonisen,[20] were of potential infectious origin, whether the patient was hospitalized or not. Culture of sputum was not required in stable state.

The quality of sputum samples was assessed using the scoring system of Murray and Washington.[21] Sputum samples were processed[22] and bacterial colonies were identified by standard methods[23] in a central laboratory. All isolates were tested for antibiotic susceptibility following the CLSI (previously NCCLS) recommendations.[24] Bacterial isolates were grouped in two categories: usual pathogens, including *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*[6,7,25–29]; and non-usual pathogens, including *Pseudomonas aeruginosa* and other non-fermentative gram-negative rods (*Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*), Enterobacteriaceae (*Klebsiella pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, *Enterobacter cloacae*, *Serratia marcescens* and *Morganella morganii*), *Corynebacterium* spp. (*Corynebacterium striatum* in almost all isolates), methicillin-resistant *Staphyloccocus aureus* (MRSA) and *Aspergillus* spp. Antibiotics used to treat each bacteria are listed in the online supplement (Table E2).

For the analysis, patients were classified in four different groups: 1) no pathogen (no pathogen isolates