Mortality of COPD Patients Infected with Multi-Resistant *Pseudomonas aeruginosa*: A Case and Control Study


Abstract

**Background:** The incidence of infections caused by multi-resistant *Pseudomonas aeruginosa* (MDRP) is increasing, especially in critically ill patients. The relevance of MDRP in the prognosis of chronic obstructive pulmonary disease (COPD) acute exacerbation in patients admitted to the hospital’s general ward is not well known.

**Patients and Methods:** Case and control study. Cases were patients admitted for COPD acute exacerbation in which a MDRP was isolated from spontaneous sputum. MDRP was defined as the absence of susceptibility to three or more antibiotic families (betalactams, quinolones, carbapenems and aminoglycosides). Patients currently or previously admitted to the intensive care unit (ICU), who had a recent surgery, neoplasia or immunosuppressive treatment were excluded from the study. Patients from the control group were admitted for COPD acute exacerbation and matched 1:1 with each case-patient in terms of age, sex, date of admission and degree of airway obstruction. *Pseudomonas aeruginosa* susceptible to all antimicrobials or other microorganisms was isolated from sputum.

**Results:** During the study period (2000–2005), 50 case-patients and 50 controls were included. Crude mortality at 2 years was 60% for the case-patients and 28% for the control group. In the logistic regression analysis adjusted for age, FEV1 and number of previous hospital admissions, MDRP infection was associated to an increased mortality in comparison to patients without MDRP (OR = 6.2; IC 95%: 1.7–22.1; p < 0.01).

**Conclusions:** In COPD patients admitted to the general ward, acute exacerbation with MDRP in sputum was associated with higher mortality.

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Introduction

*Pseudomonas aeruginosa* (Pa) is a non-fermentative gram-negative bacillus that is normally found in nature and in the hospital setting. Its capacity to grow rapidly in the environment and in the hospital setting is one of the main causes for severe nosocomial infections [1, 2]. Another important problem related to Pa infections is the recurring and fast acquisition of resistance to one or various antimicrobial agents at the same time [3–5]. Several factors have been associated with the onset and relapse of MDRP infection such as underlying chronic diseases, immunosuppression and neoplasias. Other related diseases are pulmonary, like cystic fibrosis or chronic obstructive pulmonary disease (COPD) [6, 7]. Among the most common risk factors for MDRP colonization or infection are the diagnostic or therapeutic procedures used (invasive and non-invasive) [8–10] long hospital stay, systemic steroid treatment and multiple antibiotic therapy. As regard antibiotic treatment, the previous administration of quinolones, carbapenems and betalactams [11–14] has been identified as an independent risk factor. *Pseudomonas aeruginosa* colonization has been associated with COPD acute exacerbation [15]. The isolation of this microorganism is relatively frequent and it has been found in 6%–9% of COPD acute exacerbation cases [15, 16]. *Pseudomonas aeruginosa* has also been related to a severe reduction in lung function [17, 18]. In the last few years, an increase in the prevalence of MDRP infections has been observed, especially in the critically ill patients [19], however, the prognostic significance of acute exacerbation of COPD in patients admitted to a general ward has not yet been established.
Patients and Methods

Study Design

MDRP was isolated from sputum in 91 patients with acute exacerbation of COPD throughout the study period (2000–2005). The patients included in the case – control study were patients; in whom the first isolation of MDRP was at the years: 2001, 2002, and 2003. The criteria to choose these patients were to have an adequate time of follow-up after discharged from conventional hospital ward. The duration of follow-up was until May 2006. In relation to the 41 cases who were not included in the study, 4 has been lost of follow-up, 5 did not fulfilled the inclusion criteria (had another condition or another pathogen was isolate from sputum), and the remaining 32 patients have insufficient time of follow-up.

Definition of Case-patients

Patients who fulfilled the clinical and functional criteria for COPD [20], admitted to a general ward due to acute exacerbation. The acute exacerbation was defined as having at least two major symptoms (i.e., increased dyspnoea, increased sputum purulence, or increased sputum volume), or one major and one minor symptom (i.e., nasal discharge/congestion, wheeze, sore throat, or cough) for at least two consecutive days [21] and in which a MDRP was the only pathogen identified in one or more samples of spontaneous sputum. Among the exclusion criteria were previous or current admission to the intensive care unit (ICU), any recent surgical procedure, cancer or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]). Patients with pneumonia and bronchiectasis were also excluded by clinical and chest X-rays criteria.

Definition of Controls

Patients who fulfilled the clinical and functional criteria for COPD, admitted to a general ward due to acute exacerbation but with no MDRP isolated in any spontaneous sputum. Those patients in whom the presence of a susceptible Pa was identified or had any other bacteria were also eligible as controls. The patients of the control group were matched in a proportion 1:1 with each case-patient on the variables of age, date of admission and degree of airway obstruction. The exclusion criteria were the same ones as in the case-patients group.

Collection Techniques and Culture of Sputum

The samples of respiratory secretions were collected from spontaneous sputum using the usual techniques and were cultured in McConkey, chocolate-agar, blood agar and Saboureaud agar culture media. Antibiotic susceptibility: once the microorganism was isolated and identified, all samples were studied for antibiotic susceptibility by diffusion method. 
Pseudomonas aeruginosa was defined as multiresistant when the absence of susceptibility to three or more antibiotic families usually evaluated (betalactams, quinolones, carbapenems, and aminoglycosides) was confirmed.

Statistical Analysis

Demographic characteristics (age, sex), pulmonary function expressed as FEV1, number of hospital admissions before MDRP diagnosis or other microorganisms in the control group and number of admissions after MDRP or other microorganisms diagnosis in the case and control group, respectively, were analyzed. Continuous quantitative variables were expressed as mean ± SD. The statistical analysis was carried out using the χ2-test for the comparison of proportions and the T-Student test for the comparison of quantitative variables. A p < 0.05 value for a bilateral contrast was considered statistically significant. Crude mortality was analyzed in both groups of patients at 2 years of follow-up. A multiple logistic regression model was done using mortality as a dependent variable and as co-variables the presence of MDRP, age, severity of COPD (considered by FEV1) and the total number of previous admissions of both controls and case-patients.

Results

During the study period (2000–2005), 3,221 patients required hospitalization in our centre for COPD acute exacerbation, MDRP was isolated from sputum in 91 patients (2.82%). In the present study, 50 case-patients and 50 controls were included. The case and control patients were individual patients, not episodes of acute exacerbation. The descriptive analysis of the two groups is shown in table 1.

On the topic of resistance, our results show that 30 (60%) patients had a MDRP infection with the same antibiogram. Specifically, this was defined as resistance to all the antibiotic groups usually tested (betalactams, quinolones, carbapenems and aminoglycosides) with the exception of amikacin and colistin. MDRP was susceptible only to colistin in four patients (8%). The resistance profile could not be matched in 16 patients (32%). About microbiological data, in the control group sensitive Pa was present in 10 (20%) patients; Haemophilus influenzae in 12 (24%); Streptococcus pneumonia in 8 (16%); other bacteria in 6 (12%) and mixed flora in 14 (28%). The consecutive sputum collection at follow-up shown that; MDRP persisted in 35 (70%) of the case-patients (median of 4 sputum culture per patient); the microbiology of sputum was highly variable in the control group.

Overall crude mortality of patients infected with MDRP was 12% at 1 month, 32% at 1 year, and 60% (30


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<tr>
<th>Table 1</th>
<th>General characteristics of patients with COPD and acute exacerbation (comparison of case-patients and controls).</th>
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<tr>
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<td>With MDRP (n = 50)</td>
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<tr>
<td>Age (years) (x ± SD)</td>
<td>69 ± 10</td>
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<tr>
<td>Male gender (N, %)</td>
<td>42 (84)</td>
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<tr>
<td>FEV1, % pred. (x ± SD)</td>
<td>33 ± 11</td>
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<td>Number of admissions, prior to inclusion median (range)</td>
<td>4.5 (0–17)</td>
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<td>Number of admissions after inclusion, median (range)</td>
<td>4 (0–16)</td>
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