Lower respiratory tract infections in chronic obstructive pulmonary disease outpatients with tracheostomy and persistent colonization by \textit{P. aeruginosa}☆

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Summary Outpatients with tracheostomy can be managed with a low risk for severe airways infections despite colonization with pathogenic bacteria. No studies have been focused on chronic obstructive pulmonary disease (COPD), a condition known for recurrent exacerbations. The aim of our study was to verify whether at follow-up in tracheostomized COPD versus other disease outpatients, persistent \textit{P. aeruginosa} colonization may influence the rate and treatment of lower respiratory tract infections (LRTI) or hospital admissions. Thirty-nine outpatients were considered: 24 were affected by COPD (age 66, 54–78 years, mean, range), 15 by restrictive lung disease (RLD) (57, 41–72 years). During an 18-month follow-up the number of LRTI per patient was not significantly different between COPD [37, 1(0–6)] and RLD [18, 1(0–5)], [total, median (range)]. Persistent \textit{P. aeruginosa} colonization 18 COPD (75%), 12 RLD patients (86%) and was not associated with an increased number of LRTI: 1(0–6) and 1(0–2), respectively. There were no differences in the number of hospital admissions: COPD 0(0–2), RLD 1(0–1), with a significant decrease versus before tracheostomy (P<0.001). In conclusion, the rate of LRTI and hospital admissions in COPD outpatients with chronic tracheostomy was low, similar to non-COPD patients and independent of \textit{P. aeruginosa} colonization.

Introduction

Bronchial microbial colonization is extremely frequent in subjects with chronic tracheostomy.1–4 One of the most represented microorganisms is \textit{P. aeruginosa}, a highly adaptable opportunistic human pathogen able to interact in a complex way with host cells in both acute and chronic airways diseases, a paradigmatic condition being cystic fibrosis.5 Pseudomonas colonization of the airways has been reported to be associated with severe bronchial obstruction6 and an increased frequency and severity of respiratory tract infections7–9 also in non-cystic fibrosis patients. Although it is a common belief that tracheostomy leads to an increased risk of respiratory infections, Harlid et al.3 clearly demonstrated that patients with...
chronic tracheostomy can be managed at home with a low risk for developing severe airways infections despite massive colonization with potentially pathogenic bacteria.

Studies in the literature report data on heterogeneous case series. Type of disease and case history might have an influence on post-tracheostomy infections, particularly in chronic obstructive pulmonary disease (COPD), a condition well known for repeated exacerbations in its course. The case series described by Harlid et al. included only two patients with COPD.

We recently reported that patients with chronic tracheostomy appear to harbour the same microbial flora and display the same type of local soluble defences, independently of the disease leading to tracheostomy. At that time we had no prospective data to demonstrate whether or not tracheostomized patients with different disease bear a different risk of lower respiratory tract infections (LRTI), particularly in P. aeruginosa carriers. The aim of the present investigation was to verify whether at follow-up in tracheostomized COPD versus restrictive lung disease (RLD) outpatients, the presence of persistent P. aeruginosa colonization may influence the rate and treatment of LRTI, either bronchitis exacerbations or pneumonia, or hospital admissions.

Methods

Study population

The study was carried out under the supervision of the institutional review board at the Scientific Institute of Rehabilitation in Veruno, Italy.

Thirty-nine outpatients with chronic tracheostomy for chronic respiratory failure were considered in a clinically stable phase: 24 were affected by COPD, diagnosed according to the American Thoracic Society standard criteria (age 66, 54–78 years, mean, range; M/F 21/3; months since tracheostomy 23, 3–62; all former smokers, except for one current smoker), 15 by pure RLD (12 thoracic wall deformities, three neuromuscular disease; age 57, 41–72; M/F, 3/12; months since tracheostomy 22, 2–68; all non-smokers). Recent antibiotic or corticosteroid treatments (<1 month prior to study) were among exclusion criteria. Among COPD patients, 14 were on assist or assist/control mechanical ventilation during the night and 10 on long-term oxygen therapy; 12 RLD patients were on assist or assist/control night-time mechanical ventilation and three on long-term oxygen therapy.

Serum albumin levels and total lymphocyte counts taken as systemic nutritional markers were in the normal range.

Patients with respiratory disorders other than COPD, infectious diseases, immunodeficiency conditions, autoimmune disorders, malignancies or clinically significant haematologic disorders were excluded.

Only steady-state pharmacologic treatment with bronchodilators was admitted as well as standard treatments in the case of chronic heart failure and diabetes (one case).

No signs of exacerbation (i.e. increase of cough, expectoration and dyspnea) were present at the moment of inclusion. Qualitative characteristics of expectoration were not taken into account because of their unreliability, since bronchial secretions in tracheostomized patients are frequently purulent or mucopurulent at baseline. The last episode of exacerbation had been reported more than 1 month before. None of the patients had been hospitalized within the previous 2 months.

During a follow-up of 18 months, the number of LRTI and hospital admissions was recorded. Pneumonia was defined in the case of an exacerbation with new infiltrate(s) at chest X-ray, when performed. The information was collected during periodical visits at our centre scheduled (primarily for changing the tracheostomy cannula) every 30 days in the first 6 months and every 30–60 days in the following year. Duration of an exacerbation was not recorded because of unreliable reporting (frequent disagreement between patient and relatives).

A retrospective count of hospital admissions was performed on file records focusing on the 18 months before tracheostomy.

The global number of antibiotic courses was recorded in the same follow-up period. According to patients’ report, antibiotic prescriptions were classified as appropriate, when signs of exacerbations were evident (worsening of dyspnea and productive cough), and not appropriate, when made on the basis of the microbiological data, but without signs of exacerbation (i.e. “for prevention” or to eradicate airways bacteria). Antibiotics given for non-respiratory infections were registered too, but were not included in the statistical evaluation. The choice of the antibiotic was at the general practitioner’s discretion, but generally based on the antibiogram of the most recent microbiological test on tracheobronchial aspirate. Oral or parenteral corticosteroid courses during an exacerbation were also registered.
Bronchial aspirates and processing of specimens

Tracheobronchial secretions were aspirated mechanically in sterile Luken's containers (Vygon, Ecouen, France) through a sterile catheter inserted in a sterile inner cannula.

All patients had repeated samplings at monthly intervals for 6 months to evaluate the variations of the bronchial flora. In the following months, microbiological evaluations were carried out on request of the family doctor for clinical purposes, i.e. targeted antibiotic therapy in case of an exacerbation.

Bacteriological evaluations

Bacterial counts were assessed with the method of serial dilutions with saline (10^{-4}–10^{-7} by serial 10-fold dilutions of the original sample). The medium used was sheep blood agar. Data are reported as colony forming units (CFU)/ml. When a single strain is not specified, as in the case of multiple isolations, CFU refers to the highest charge independent of the type of bacteria isolated.

Identification of bacterial strains was performed with routine methods: rapid ID 32 STREP for Streptococccaeae, ID 32 STAPH for the genera Staphylococcus, API NH for Neisseria, Haemophilus and Branhamella catarrhalis, ID 32 E for Enterobacterianeae and other Gram-negative rods, and ID 32 C for yeasts (bioMérieux sa, Marcy-l'Etoile, F).

Anaerobe bacteria were not assessed. Persistent colonization was defined as three or more consecutive isolations of the same bacterial strain.

Statistical analysis

Data are reported as geometric mean and range or median and range, unless otherwise specified. The Mann–Whitney U test or Student t-test were used for examining differences between unpaired categorical or numerical data. Frequency distributions were compared by chi-square contingency tests with continuity correction. Regression analysis was applied to study the correlation between bacterial charge and number of exacerbations.

A 95% probability was considered statistically significant. Analyses were performed using a microcomputer (Macintosh LC) and Stat-view + Graphics software (Abacus Concept).

Results

One patient with RLD and one patient with COPD died at home after 1 and 12 months, respectively, for unknown cause. One RLD patient was lost to follow-up after 4 months for lack of cooperation.

The number of LRTI per patient was not significantly different between COPD and RLD patients: 37, 1(0–6) and 18, 1(0–5), [total, median (range)], respectively.

Persistent colonization with P. aeruginosa was found in 18 COPD (75%) and 12 RLD patients (86% of 14, excluding one patient who died after 1 month to whom the definition of persistent colonization could not be applied). Occasional isolation occurred in four COPD and two RLD patients. Therefore, in only two COPD and one RLD patients was P. aeruginosa never isolated. Patients with or without persistent colonization had a similar number of LRTI, 1(0–6) and 1(0–2), respectively, P = 0.5, Mann–Whitney U-test. We found no correlation between bacterial load and number of exacerbations. Only in one patient with COPD did chest X-ray document pneumonia.

Type and prevalence of bacterial isolates is shown in Fig. 1 for the two groups of patients separately (only the five main strains). Over 6 months the number of isolates for each of the main strains remained quite stable, in particular for P. aeruginosa, despite intercurrent antibiotic courses. Bacterial load variations for the two main bacterial strains, P. aeruginosa and S. marcescens, are shown in Table 1. We found no correlation between bacterial load and months since tracheostomy. Results of tests for antibiotic sensitivity are reported in Table 2 limited to the two main strains isolated and to baseline versus final evaluations. No particular variations were noted with the exception of an increased resistance to imipenem/cilastatin and non-protected piperacilline. This last agent had been used at home in a number of cases, at a dose lower than recommended, while no domiciliary administration of imipenem/cilastatin was registered.

At follow-up the number of antibiotic courses did not differ in the two groups: COPD 67, 2(0–11), RLD 26, 2(0–5) [total, median (range)], including antibiotics administered for non-respiratory infections (8 and 4 courses, respectively). A significantly higher number of inappropriate antibiotic courses was prescribed in COPD patients [22, 1(0–4)], reportedly justified for preventive purposes, i.e. based on microbiological results, but in the absence of clinical exacerbation, as compared with RLD patients [4, 0(0–1)], P = 0.02. There was a significant positive correlation between number of
Table 1  Bacterial load variations over time for the two strains, *P. aeruginosa* and *S. marcescens*, accounting for most isolations (geometric mean and range).

<table>
<thead>
<tr>
<th>Months</th>
<th><em>P. aeruginosa</em></th>
<th><em>S. marcescens</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>$3.8 \times 10^5$ ($10^3-4.2 \times 10^7$)</td>
<td>$3.1 \times 10^5$ ($3 \times 10^3-1.6 \times 10^7$)</td>
</tr>
<tr>
<td>1</td>
<td>$2.9 \times 10^5$ ($3 \times 10^3-1.6 \times 10^7$)</td>
<td>$2.8 \times 10^5$ ($3.7 \times 10^3-5.7 \times 10^5$)</td>
</tr>
<tr>
<td>2</td>
<td>$8.3 \times 10^5$ ($1.5 \times 10^4-2.8 \times 10^7$)</td>
<td>$2.1 \times 10^5$ ($10^4-1.7 \times 10^7$)</td>
</tr>
<tr>
<td>3</td>
<td>$1.0 \times 10^6$ ($10^3-7.2 \times 10^7$)</td>
<td>$3.1 \times 10^5$ ($10^4-2.0 \times 10^6$)</td>
</tr>
<tr>
<td>4</td>
<td>$9.4 \times 10^5$ ($3.5 \times 10^4-5.4 \times 10^7$)</td>
<td>$3.4 \times 10^5$ ($10^4-1.8 \times 10^7$)</td>
</tr>
<tr>
<td>5</td>
<td>$5.3 \times 10^5$ ($7.5 \times 10^3-6.0 \times 10^7$)</td>
<td>$2.6 \times 10^5$ ($3 \times 10^3-9.9 \times 10^6$)</td>
</tr>
<tr>
<td>6</td>
<td>$2.0 \times 10^6$ ($2.9 \times 10^3-7.6 \times 10^7$)</td>
<td>$3.2 \times 10^5$ ($10^4-1.3 \times 10^6$)</td>
</tr>
</tbody>
</table>

Table 2  Patterns of antibiotic resistance as percent prevalence of resistant among total strains isolated from the 39 patients under study at baseline (T0) and after 6 months (T6).

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th><em>P. aeruginosa</em> (26/33)</th>
<th><em>S. marcescens</em> (20/22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% T0/% T6</td>
<td>% T0/% T6</td>
</tr>
<tr>
<td>Ticarcilline</td>
<td>15.4/9.1</td>
<td>40/36.4</td>
</tr>
<tr>
<td>Ticarcilline/clavulanate</td>
<td>11.5/3</td>
<td>0/4.5</td>
</tr>
<tr>
<td>Piperacilline</td>
<td>11.5/21.2</td>
<td>40/40.9</td>
</tr>
<tr>
<td>Piperacilline/tazobactam*</td>
<td>3.8/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>11.5/6.1</td>
<td>15/13.6</td>
</tr>
<tr>
<td>Cefsulodine</td>
<td>23.1/18.2</td>
<td>95/95.5</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>11.5/9.1</td>
<td>40/31.8</td>
</tr>
<tr>
<td>Imipenem/cilastatin</td>
<td>19.2/36.4</td>
<td>0/9.1</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>46.2/30.3</td>
<td>65/63.6</td>
</tr>
<tr>
<td>Amikacin</td>
<td>0/3</td>
<td>5/9.1</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>42.3/30.3</td>
<td>0/0</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>38.5/30.3</td>
<td>65/63.6</td>
</tr>
<tr>
<td>Colistin</td>
<td>3.8/6.1</td>
<td>95/90.9</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>26.9/18.2</td>
<td>0/0</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>73.1/48.5</td>
<td>5/0</td>
</tr>
</tbody>
</table>

Only the two main bacteria have been considered (no. of isolates in brackets, baseline/6th month).

*Tested in 13 patients only.*
LRTI and frequency of inappropriate antibiotic courses \( (r = 0.64, r^2 = 0.41, P = 0.002) \). Corticosteroids by general administration were used in only four COPD patients.

There were no differences in the number of hospital admissions before tracheostomy between COPD, 2(0–4), median(range), and RLD patients, 2(1–4). The same was true for the follow-up period of this study: COPD 0(0–2) versus RLD 1(0–1), but with a highly significant decrease in the number of post-tracheostomy hospitalizations compared to pre-tracheostomy \( (P < 0.001) \). Analysis of hospital admissions using the criterion presence/absence of persistent \( P. \) aeruginosa colonization did not give significant results.

Interestingly, the total number of LRTI was even lower \( (P < 0.05) \) than the number of pre-tracheostomy hospital admissions, that to a certain degree reflects the number of severe LRTI.

The comparison of data concerning all the patients on mechanical ventilation versus all those on long-term oxygen therapy did not reveal significant differences in prevalence or charge of \( P. \) aeruginosa, number of LRTI and hospital admissions or antibiotic courses.

**Discussion**

Previous studies demonstrated that Pseudomonas colonization is associated with an increased frequency and severity of LRTIs, particularly in the acute setting\(^8\),\(^9\) and in subjects with cystic fibrosis,\(^5\) but also in long-term tracheostomy patients.\(^7\) In our study, most patients showed persistent colonization with \( P. \) aeruginosa, but this condition was not associated with an increased number of LRTI. Our study confirms also for outpatients with COPD, a condition known for recurrent respiratory infections, that tracheostomy is not a major risk factor for respiratory infections despite heavy bacterial colonization of the large airways.\(^3\) Data favourably compare with the average of two episodes per year in moderate-to-severe COPD patients without tracheostomy reported in the literature.\(^6\) Even better, number of hospital admissions were significantly decreased in our tracheostomized COPD patients with respect to before tracheostomy. No differences were found in number of hospitalizations with regard to type of disease (COPD or RLD) or \( P. \) aeruginosa colonization. It may be argued that a bias exists with regard to regular as compared to “on demand” visits, but to counter this would require a control group with substitution of the tracheal cannula at random intervals, a protocol ethically difficult to accept. Our data are somewhat different from those reported by Niederman et al. in subjects with long-term tracheostomy,\(^7\) the most likely explanation being the in-hospital setting of their study.

Although bacterial infection is one of the main causes of exacerbations in patients with chronic respiratory failure, COPD in particular,\(^11\) it must be pointed out that the term exacerbation does not necessarily imply bacterial infection. On the other hand, in presence of chronic bacterial colonization a definite causative link between bacteria and an exacerbation is quite difficult to prove. For clinical decision-making this is an important problem and therapy is in fact often empirical.

Four COPD patients received either oral or parenteral corticosteroids. The number of subjects is too low to infer any conclusion about the influence of corticosteroids on bacteria-host interaction or clinical data at follow-up.

Early antibiotic treatment can be clinically significant in exacerbated severe patients,\(^12\) such as those with chronic respiratory failure, but in our study 28% of prescriptions were inappropriate (i.e. only based on microbiological data, in absence of clinical modifications). Persistent \( P. \) aeruginosa colonization did not influence the rate of prescription. It may be argued that we do not know whether the number of exacerbations in COPD patients was not significantly higher precisely thanks to preventive antibiotic treatment. Against this argument is the positive correlation between number of LRTI and frequency of inappropriate antibiotic courses: we would actually expect a negative correlation should antibiotics be really effective in preventing exacerbations or no correlation if the two variables are indifferent. An alternative interpretation is that patients with a history of frequent LRTI are more likely to be prescribed an antibiotic course, even in the case of clinical stability, when sputum analysis is available introducing a bias towards intervention.

We have already commented on the pattern of antibiotic resistance in our tracheostomized patients in a previous paper.\(^4\) The only important variations in time were found for imipenem/cilastatin and non-protected piperacilline; in the latter we were able to document administration at home at inappropriate doses, while imipenem/cilastatin was probably used during hospital stay at centres other than ours. The relative stability of bacterial isolates and antibiotic sensitivity patterns together with clinical findings led to a remarkable modification in our long-term management strategy for tracheostomized patients. Although beyond the scope of this paper, it is worth reporting that one of
the practical consequences of this study was an agreement with family doctors to carry out microbiological evaluations only in the case of clinical deterioration, avoiding any attempt to eradicate simple airways colonization. This has led to a sharp reduction in microbiological evaluations and preventive antibiotic courses, without any increase in the frequency of LRTI and hospital admissions.

These data may be an important aid in deciding about tracheostomy as a therapeutic option for severe COPD and in formulating a correct antibiotic policy. At the same time, our results stimulate further research on the factors that differentiate bacteria–host interaction in the acute and chronic conditions. As an example, comparison between virulence intrinsic characteristics or DNA fingerprinting of pseudomonas strains responsible for nosocomial infections and strains simply colonizing the airways is worth investigation, because patients with chronic colonization may represent an important source of cross-contamination in case of hospital admission. Furthermore, airways defence mechanisms in chronic patients may help in finding new modalities of prevention and treatment for the acute infections.

In conclusion, the rate of LRTI and hospital admissions in COPD outpatients with chronic tracheostomy was low, similar to non-COPD tracheostomized patients and independent of persistent P. aeruginosa colonization.

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References