Pseudomonas aeruginosa in patients without cystic fibrosis is strongly associated with chronic obstructive lung disease

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ABSTRACT

INTRODUCTION: The objective of this study was to investigate the occurrence and consequences of *Pseudomonas aeruginosa* infection in a group of non-cystic fibrosis (CF) patients with regard to clinical presentation, treatment and change in lung function.

MATERIAL AND METHODS: This was a three-year retrospective study of 113 patients with *P. aeruginosa*-positive airway samples achieved from the Department of Clinical Microbiology, Aarhus University Hospital, Denmark. Medical records were reviewed in order to register patient demographics, symptoms, co-morbidity, pulmonary function tests (PFT), treatment, X-ray/computed tomography findings and mortality. Finally, deterioration of lung function was evaluated by comparing the first and last available PFT in the period of observation.

RESULTS: Most patients had several co-morbidities and only seven patients had none. 62% had a diagnosis of chronic obstructive pulmonary disease (COPD). We found a significant decrease in lung function within the observation period among patients with *P. aeruginosa*-infection as evidenced by all measured PFT-parameters except the forced expiratory volume in the first second/forced vital capacity-ratio. A total of 27 patients (24%) died within the observation period.

CONCLUSION: *P. aeruginosa* is an opportunistic bacterium infecting primarily patients with severe lung disease. Our data show a significant reduction in lung function among *P. aeruginosa*-positive non-CF patients over a three-year period of time. The reduction, however, is not different than otherwise reported in COPD patients in general leading to no conclusion as to whether this pathogen is a marker of disease progression or the cause for progression itself.

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Pseudomonas aeruginosa is a Gram-negative bacillus belonging to the family of *Pseudomonadaceae*. Despite being an aerobic organism, *P. aeruginosa* can adapt to conditions of partial or total oxygen depletion. Adaptation to microaerobic or anaerobic environments is essential for *P. aeruginosa* during lung infection in cystic fibrosis (CF) patients, where thick layers of lung mucus and alginate surrounding mucoid bacterial cells, also known as biofilm, can limit the diffusion of oxygen [1].

P. aeruginosa has long been recognized to be the main pathogen in the development, prognosis and outcome in patients with CF [2, 3]. Disease-specific lung alterations in CF-patients facilitate opportunistic colonisation by environmental *P. aeruginosa*, that later convert to mucoid strains exhibiting phagocytotic resistance and increased tolerance to antibiotics. Valderrey et al described similar colonisation patterns in patients with bronchiectasis (BS) and in CF patients with respect to clonal persistence and dominancy. Their cohort of patients with chronic obstructive pulmonary disease (COPD) was too small to demonstrate the same pattern, but data suggested that patients with COPD suffer from chronic colonisation by *P. aeruginosa* as well [2]. Also, studies in patients with BS have shown that patients with *P. aeruginosa*-positive sputum culture have lower pulmonary function, quality of life scores and more symptoms and hospital admittances, which may very well apply to COPD patients as well [4].

In the present study, we wished to investigate the occurrence and possible consequences of *P. aeruginosa*-infection in a group of non-CF patients with regard to clinical presentation, treatment and change in lung function.

MATERIAL AND METHODS

The study was conducted as a retrospective case series. All respiratory tract specimens with growth of *P. aeruginosa* from 1 January 2006 to 31 December 2008 (n = 1,142) were identified in the laboratory information system at the Department of Clinical Microbiology, Aarhus University Hospital. After exclusion of 587 samples from patients with CF, 553 *P. aeruginosa*-positive samples from 246 patients were available for analysis. The medical records of these 246 patients were reviewed retrospectively in order to register patient characteristics, symptoms, co-morbidity, pulmonary function tests (PFT), treatment with inhaled corticosteroids (ICS), oral corticosteroids (OCS), preceding antibiotic treatment within 30 days of positive *P. aeruginosa* growing/culture, promixin-inhalations, antibiotic treatment of *P. aeruginosa*, pathological findings on chest X-ray and/or

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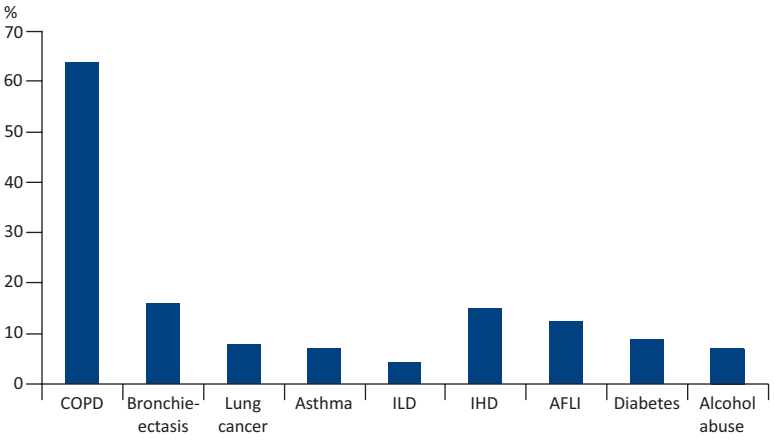
computed tomography (CT) of thorax, number of lung disease-related admissions and mortality. Finally, deterioration of lung function was evaluated by comparing the change in forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC)-values from the first and last performed PTF in the period of observation. The minimal acceptable time span between two PFTs was set to six months. A six-month interval was chosen to avoid the daily variability in lung function measurements and to detect a possible decline in lung function.

The exclusion criteria were: CF, lung transplantation, conditions with compromised airways (ventilator treatment/airway intervention, airway compromised due to neuromuscular disorder) and immune defects, since these conditions increase the risk of infection. Patients with lung transplantation due to concurrent immunosuppression and impaired clearance mechanisms were also excluded. Patients with compromised airways following ventilator treatment/airway intervention have an increased risk of infection due to airway intervention/endotracheal intubation and mechanical ventilation [5]. Patients with neuromuscular disease have increased infection susceptibility following ventilator treatment/airway intervention and impaired airway clearance in general, which is also the case for patients with immunodeficiency such as haematological disease or those taking immunomodulating drugs other than ICS and OCS, since these medications were under investigation. Patients dying within the observational period were not excluded.

Trial registration: not relevant.

FIGURE 1

Co-morbidities.



AFLI = atrial fibrillation; COPD = chronic aobstructive pulmonary; IHD = ischaemic heart disease; ILD = interstitial lung disease.

TABLE 1

Characteristics of 113 patients with *Pseudomonas aeruginosa*-positive airway samples.

Age, yrs, mean (SD)	67 (13)
Gender, M/F, n	57/56
Never smokers, n (%)	7 (9)
Increased sputum, n (%)	64 (79)
Sputum purulence, n (%)	53 (71)
SOB, n (%)	68 (80)
LTOT, n (%)	30 (27)
ICS, n (%)	86 (76)
OCS, n (%)	60 (53)
Preceding AB, n (%)	46 (41)

ICS = inhaled corticosteroids; LTOT = long-term oxygen treatment; OCS = oral corticosteroids; Preceding AB = preceding antibiotic treatment within 30 days of positive *P. aeruginosa* growing/culture; SD = standard deviation; SOB = shortness of breath.

Statistics

Patient characteristics are presented as proportions. The relative risk between groups of *P. aeruginosa*-positive non-CF-patients (n = 246) stratified according to dead or alive was calculated and the χ^2-test was used to determine whether there was a statistically significant difference between the groups.

PFT-values are presented as mean (standard deviation) since they are known to have uniform variance and hence follow the normal distribution [6]. We confirmed this fact by generating histograms that followed the normal distribution.

Calculation of the means of change in PFT-values in the same group of patients over time was conducted using a two-tailed paired t-test. These data are presented as mean values with 95% confidence intervals and corresponding p-value.

Comparison of mean PFT-values between living and dead patients and calculation of the corresponding p-values were conducted using a t-test assuming unequal variances in accordance to calculated F-test.

A two-sided p-value < 0.05 was considered statistically significant. Microsoft Excel 2003 was used for all analyses.

RESULTS

Of the primary selected 246 non-CF patients with *P. aeruginosa*-positive airway samples, 133 were excluded from analysis. The reasons for their exclusion were ventilator treatment/airway intervention (n = 79), airway compromised due to neuromuscular disorder (n = 29), immune defect (n = 14), lung transplantation (n = 6) and missing medical records/lack of information (n = 5). The 79 patients excluded due to ventilator treatment/airway intervention belonged to various specialties such as ab-

TABLE 2

Pulmonary function tests of the study population.

PFT	Mean (SD)	Patients, n
FEV1	1.17 l (0.78 l)	88
FEV1(%)	44.9% (24.6%)	79
FVC	2.26 l (0.96 l)	62
FVC(%)	64.2% (22.5%)	60
Ratio	0.55 (0.18)	62

FEV1 = forced expiratory volume in the first second; FEV1(%) = forced expiratory volume in the first second per cent predicted; FVC = forced vital capacity; FVC(%) = forced vital capacity per cent predicted; PFT = pulmonary function test; Ratio = FEV1/FVC; SD = standard deviation.

dominal surgery, neurosurgery and mixed intensive care unit. The characteristics of the remaining 113 patients are shown in **Table 1**.

Samples were distributed evenly throughout the observation period with 63 samples in 2006, 89 in 2007 and 85 in 2008. We found no seasonal variance, with 49% of the samples being collected during winter (October through March).

Samples consisted of airway sputum (n = 215) and bronchoalveolar lavage fluid (n = 22). A total of 53 patients had two or more *P. aeruginosa*-positive samples. Of the patients producing multiple *P. aeruginosa*-positive samples, only 22 were produced with more than a six-month time span. In all, 27 patients (24%) died within the observation period. At least six (24%) of these patients died of pneumonia within a week without identification of other microbial agents and were as such considered to die from a *P. aeruginosa*-pneumonia.

Figure 1 shows co-morbidities available from journal records. Most patients had several co-morbidities and only seven patients had none. Four of these, however, showed an obstructive pattern in PFT. 62% had a COPD diagnosis.

We were able to retrieve FEV1 from 88/113 patients as shown in **Table 2**. Mean forced expiratory volume in the first second per cent predicted (FEV1(%)) was 45% which in combination with a significant mean FEV1/FVC-ratio of 0.55 corresponded to obstruction due to severe COPD.

A total of 52 patients completed two PFTs separated by six months or more within the observation period (median time span 26 months, range 6-34 months). As seen in **Table 3**, we found a significant decrease in lung function among patients with *P. aeruginosa*-infection as evidenced by all measured PFT volumes.

Due to the considerable amount of patients dying within the observation period (24%), we chose to conduct a dead versus live patient comparison.

As seen in **Table 4**, we found a male preponderance and more frequent use of oral corticosteroids and antibiotic treatment within the group of patients dying in the observation period. Lung cancer was six times more frequent in the dead than in the living patients. Ischaemic heart disease was more than twice as common among the dead patients.

Pulmonary function parameters were reduced in both groups. We found a significantly lower FEV1, FEV1(%) and ratio in the dead patients group.

As to treatment of the *P. aeruginosa*-pneumonia, we found no difference between the two groups. Less than 60% of patients colonised with *P. aeruginosa* received antibiotic treatment with activity against *P. aeruginosa*. Approximately only one out of four received antibiotics with the purpose of *P. aeruginosa* eradication.

CT/High Resolution CT was available in 79 patients in whom 58 (73%) had bronchiectases and 43 (54%) had pulmonary opacities. The 113 patients had taken a total of 797 chest-X-rays in which 235 (29%) showed an infiltrate.

DISCUSSION

To the best of our best knowledge, the present study presents the first report on the epidemiology of non-compromised airway, immune-competent non-CF patients with a positive *P. aeruginosa* airway culture.

Our study has confirmed that *P. aeruginosa* is a bac-

TABLE 3

Change in pulmonary function tests within the observation period.

	Patients, n	Start , mean (SD)	End, mean (SD)	Change	95% CI	p-value
FEV1	52	1.23 l (0.80 l)	1.12 l (0.86 l)	–0.10 l	–0.20–-0.01 l	0.028
FEV1(%)	49	47.4% (26.0%)	42.6% (24.5%)	–4.07 %-points	–7.98–-0.15 %-points	0.042
FVC	41	2.27 l(0.89 l)	1.94 l (1.01 l)	–0.43 l	–0.69–-0.16 l	0.002
FVC(%)	41	65.4% (22.3%)	56.1% (25.4%)	–12.91 %-points	–21.12–-4.69 %-points	0.003
Ratio	41	0.56 (0.19)	0.58 (0.19)	–0.03	–0.10-0.04	0.326

CI = confidence interval; FEV1 = forced expiratory volume in the first second; FEV1(%) = forced expiratory volume in the first second per cent predicted; FVC = forced vital capacity; FVC(%)= forced vital capacity per cent predicted; PFT = pulmonary function test; Ratio = FEV1/FVC; SD = standard deviation.

TABLE 4

Patient characteristics, co-morbidities, pulmonary function and treatment in the group of patients who died (Dead) respectively did not die (Live) within the observation period.

	Dead	Live	Difference	RR	p-value
Patient characteristics					
Patients, n	27	86	–	–	–
Age, yrs, mean	69	66	–	–	–
Male proportion, %	67	44	–	1.51	0.012
LTOT, %	33	24	–	1.37	0.208
ICS, %	63	72	–	0.87	0.619
OCS, %	59	40	–	1.50	0.025
Preceding AB, %	52	24	–	2.12	0.003
Co-morbidities					
COPD, %	63	64	–	0.98	0.509
Bronchiectasis, %	4	20	–	0.19	0.064
Lung cancer, %	22	3	–	6.37	0.001
Asthma, %	7	7	–	1.06	0.629
ILD, %	4	5	–	0.80	0.649
IHD, %	26	12	–	2.23	0.041
AFLI, %	15	12	–	1.27	0.454
Diabetes, %	4	10	–	0.35	0.298
Alcohol abuse, %	7	7	–	1.06	0.629
Pulmonary function					
FEV1, l, mean (SD)	0.86 (0.34)	1.15 (0.84)	–0.29	–	0.003
FEV1(%), mean (SD)	34.2 (18.4)	47.1 (25.3)	–12.9	–	0.032
FVC, l, mean (SD)	2.05 (0.65)	2.32 (1.03)	–0.27	–	0.238
FVC(%), mean (SD)	56.5 (16.8)	66.4 (23.5)	–9.9	–	0.100
Ratio, mean (SD)	0.45 (0.15)	0.59 (0.18)	–0.14	–	0.008
Treatment					
Any treatment, %	59	58	–	1.02	0.444
Pseudomonas aeruginosa eradication[a], %	15	29	–	0.51	0.194
Other treatment, %	44	29	–	1.53	0.648

AFLI = atrial fibrillation; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in the first second; FEV1(%) = forced expiratory volume in the first second per cent predicted; FVC = forced vital capacity; FVC(%) = forced vital capacity per cent predicted; ICS = inhaled corticosteroids; ILD = interstitial lung disease; LTOT= long-term oxygen treatment; OCS = oral corticosteroids; Preceding AB = preceding antibiotic treatment within 30 days of positive *P. aeruginosa* growing/culture; Ratio = FEV1/FVC; RR = relative risk; SD = standard deviation.
a) *P. aeruginosa* eradication regimen: 2 weeks intravenous treatment with piperacillin-tazobactam in combination with oral ciprofloxacin.

terium most often identified in the severely ill patients [7]. More than half of our patients with a *P. aeruginosa* culture-positive sputum either had compromised airways (mostly ventilator treatment) or immune deficiencies. Patients excluded on the basis of ventilator treatment/airway intervention belonged to a broad range of specialities which underlines the well-known affinity of *P. aeruginosa* to foreign bodies [7] rather than giving rise to speculation about selection bias.

Of the 113 patients participating in our study, 94% suffered from co-morbidities; more than 60% had COPD and almost 20% also had a confirmed diagnosis of BS. Many patients were treated with either ICS or OCS, and this may add to *P. aeruginosa* susceptibility by inhibition of normal immune defence mechanisms.

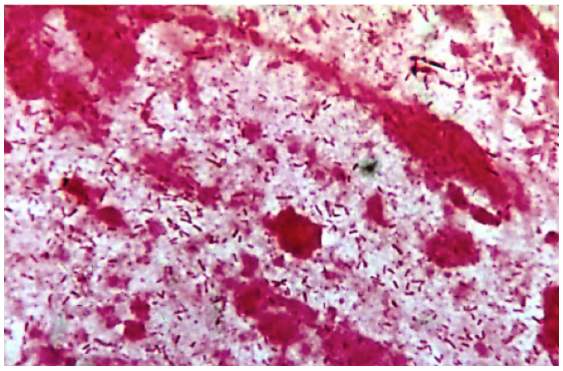
Earlier studies have shown that 29-50% of COPD patients have BS and by evaluation of 79 available chest CTs, we confirmed that most COPD patients (corresponding to 73% of the *P. aeruginosa*-positive patients) had BS. Thus, the main part of *P. aeruginosa*-positive patients had either COPD and/or BS, although other co-morbidities also were common.

It has been questioned whether *P. aeruginosa* is a marker of disease severity and as such an innocent bystander, or whether colonisation/infection per se worsens the pulmonary function and the prognosis. *P. aeruginosa* has previously been shown to infect patients with extensive pulmonary disease and severe airflow obstruction [8], and two studies have shown that infection leads to an increased progression of disease with a more rapid decline in lung function parameters [9, 10].

We did find a significant deterioration in pulmonary function among non-CF *P. aeruginosa*-patients with a FEV1 and FVC reduction of 0.10 l and 0.43 l, respectively, during a median time span of 26 months. However, it is important to appreciate that our data should be interpreted with reservations. Very low pulmonary function tests and the lack of standardization in regard to patent conditions (exacerbation/no-exacerbation) reduce validity. Moreover, the significant reduction should a priory be compared to the disease-specific deterioration in pulmonary function among COPD patients. According to the Global Initiative for Obstructive Lung Disease (GOLD), the mean severity of COPD in our patients is considered severe (GOLD stage III: Severe COPD. FEV1% 30-49% of predicted). In a recent review [11], the mean FEV1 decline among GOLD stage III COPD patients was reported to be 38-59 ml/year. Vestbo et al found a decline of 33 ml/year among GOLD stage III patients in a three-year multicentre study of 2,163 COPD patients [12]. These numbers taken into consideration, the significant reduction in lung function among our patients should probably be ascribed to COPD rather than the *P. aeruginosa*-colonisation/infection.

Certainly, patients prone to *P. aeruginosa*-infection suffered from severely reduced lung function. Aside from this, they seemed to have a range of other serious health conditions with increased mortality such as ischaemic heart disease, atrial fibrillation, diabetes and alcohol abuse. Of the 113 eligible patients, 24% died within three years of observation. Analysis of co-morbidities revealed the high mortality rate to be due to mainly lung cancer and ischaemic heart disease. Loebinger et al have shown an independent effect of *P. aeruginosa* on mortality in patients with BS [13]. This finding is not supported by our data.

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study found a 10% mortality in COPD patients within three years of observation. The ECLIPSE study population, however, was



Mucus with partially autolysed leukocytes and Gram-negative rods = Pseudomonas aeruginosa-pneumonia (Gram stain × 1,000) (Photo: *Niels Høiby*).

only 40-75 years old and had no other respiratory disorder than COPD such as asthma, interstitial lung disease or lung cancer [14]. A younger study population and exclusion of patients with lung cancer would explain the lower mortality rate in the ECLIPSE study.

We categorised chronic colonisation as the culture of *P. aeruginosa* from sputum samples separated by more than six months. Using this criterion, only 22 of our 113 patients (19%) were chronically infected. Obviously, a proportion of the remaining 91 patients only encountered intermittent infection. However, several studies have stated that once *P. aeruginosa* has infected the lungs, they stay colonised and this gives rise to recurrent COPD exacerbations [2, 15]. This leads to the suspicion that doctors tend to lack focus on this area and hence fail to follow-up on *P. aeruginosa*-positive patients. The lack of focus is also evident in terms of treatment in our population. Less than two out of three patients with *P. aeruginosa*-infection in general received treatment and only one out of four received *P. aeruginosa*-specific therapy with piperacillin-tazobactam and ciprofloxacin with the aim of eradication.

No causal statement can be made on the basis of this retrospective study. More studies are needed to evaluate the effect of eradication therapy on pulmonary function, symptoms and prognosis. Also, treatment with inhaled promixin or tobramycin needs to be evaluated in non-CF patients. The present study strengthens the need for guidelines for management of *P. aeruginosa* in non-CF patients.

CONCLUSION

P. aeruginosa is an opportunistic pathogen thought to infect patients with severe lung disease. This is corroborated by our data which show that the characteristic pseudomonas-infected non-CF patient has severe COPD or BS, several co-morbidities and is treated with either inhaled or oral corticosteroids. We found no gender difference and almost all patients were smokers or ex-smokers. The most common symptoms observed were increased sputum, sputum purulence and shortness of breath.

Our data also show a significant reduction in lung function among *P. aeruginosa*-positive non-CF patients over a three-year period of time. The reduction, however, is not different than that otherwise reported in COPD patients in general leading; therefore, no conclusion can be made as to whether this pathogen is a marker of disease progression or the cause for progression itself.

The great diversity in regards to follow-up and treatment underscores the need for further investigation and development of guidelines for management of *P. aeruginosa* in non-CF patients.

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CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

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