Clinical course of children with chronic suppurative lung disease or bronchiectasis infected with Pseudomonas aeruginosa

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Abstract

Children with chronic wet cough and without cystic fibrosis (non-CF) may suffer from chronic suppurative lung disease (CSLD) or bronchiectasis. Pseudomonas aeruginosa (Pa) can be one of the offending microbes in these children. The present study aimed to describe the clinical course of children with the above two conditions who were infected with Pa.

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Abstract

Background/Aim: Children with chronic wet cough and without cystic fibrosis (non-CF) may suffer from chronic suppurative lung disease (CSLD) or bronchiectasis. Pseudomonas aeruginosa (Pa) can be one of the offending microbes in these children. The present study aimed to describe the clinical course of children with the above two conditions who were infected with Pa.

Methods : Data of 54 children with CSLD/bronchiectasis diagnosed and attended in our department were retrospectively analysed through a Cox proportional hazard model, with age, presence of bronchiectasis, use of inhaled colistin, azithromycin, inhaled hypertonic saline as the covariates. Disease remission was defined as the absence of daily wet cough for six months along with four negative cultures taken during the last four consecutive follow-up visits.

Results : Nebulised antibiotics and the presence of bronchiectasis were statistically significant predictors of remission (HR:3.99; 95%CI:1.12-14.14; p= 0.032, and HR:0.24; 95%CI:0.08-0.71; p= 0.010).

Conclusion : The rate of disease remission increases with the use of inhaled colistin and decreases when there is established bronchiectasis.

Chronic endobronchial infections in children not suffering from cystic fibrosis (non-CF) are characterized as chronic suppurative lung disease (CSLD) or bronchiectasis. These two conditions do not represent distinct entities but are rather parts of the spectrum of the chronic infection of conducting airways[1,2]. Their clinical characteristics are indistinguishable, with chronic wet cough being the most prominent and essential feature of both conditions. The distinction between these two otherwise similar entities is based on the chest high-resolution CT scan (HRCT) which shows dilatation of the bronchi in bronchiectasis whereas it is non-diagnostic in CSLD[1,3]. Their pathogenesis is based on Cole's vicious cycle hypothesis where an initial bacterial endobronchial infection leads to neutrophilic inflammation and impaired airway clearance that results in airway damage, further growth and spread of the bacteria, and eventually, the establishment of a chronic infection[4]. Bronchiectasis represents the latter stage of this pathological process.

Pseudomonas aeruginosa (Pa) rarely infects the lung without an underlying immunity defect or impairment of the mucociliary clearance. It is a well-known and common pathogen in cystic fibrosis (CF) especially in patients with advanced disease. It has been shown that Pa is associated with an accelerated decline of lung function, deterioration of the radiographic features, increase in the number of exacerbations, and in general, it is considered a significant indicator of the severity of bronchiectasis in both adult and pediatric patients[5-9].

The association of Pa with poor clinical outcomes renders its early detection of great importance in patients with chronic endobronchial infections. The present study aimed to describe the clinical course of non-CF children with CSLD or established bronchiectasis who were infected with Pa.

Methods

The present study was conducted in the Pediatric Pulmonology Unit of the Attikon University Hospital in Athens, which is one of the main tertiary referral centres for pediatric pulmonary disorders in Greece. We retrospectively analysed data of 54 children with CSLD/bronchiectasis, without an identifiable cause, who had been diagnosed and followed in our department. Investigations in all patients included sweat test and/or CF gene mutation analysis and measurement of serum immunoglobulins. Nasal nitric oxide test and high-speed video microscopy analysis were performed only in patients who fit the clinical phenotype of primary ciliary dyskinesia. All had Pa isolated at least once in their sputum, or cough/throat swabs, or bronchoalveolar lavage (BAL) cultures.

Data regarding the time of chronic wet cough commencement, the time of referral to our department (which coincided with the time of diagnosis of CSLD/bronchiectasis), and the duration of follow up were retrieved from the medical records. Microbiological data and the percent-predicted FEV1 (ppFEV1) values (calculated with the NHANES III reference equations) of all patients with valid spirometries were also retrieved. For the purposes of this study, disease remission was defined as the absence of daily wet cough for four months along with three negative cultures taken during the last three consecutive follow-up visits. All patients received ciprofloxacin per os for at least 3 weeks after the isolation of Pa, and started (if they had not already been on) daily chest physiotherapy. Some of them also received long term treatment with twice-daily inhaled colistin and/or thrice-weekly azithromycin and/or nebulized hypertonic saline. Three-monthly follow-up visits were arranged for all children. In all visits, sputum or cough/throat swabs cultures were obtained and spirometry was performed on all patients [?]5 years old who were able to cooperate.

Radiological records were retrospectively reviewed for the presence of bronchiectasis in chest high-resolution computed tomography (HRCT) scans which were obtained before or at about the same time with the isolation of Pa. The evaluation of the HRCT scans was performed by the pediatric radiologists of our hospital (E.A., S.P., and A.M.) who were aware of the patients' clinical history. The criteria for the diagnosis of bronchiectasis on HRCT were dilatation of bronchi with a broncho-arterial ratio > 0.80[10,11]; parallel bronchial walls in a longitudinal section (tram sign); visualization of bronchi within 1 cm of pleura. The modified Bhalla score was used to quantify the severity of bronchiectasis[12].

Statistical analysis : Variables are described as medians with interquartile range (IQR). Univariate comparisons were performed with Fisher's exact test and Wilcoxon rank-sum test. Graphical presentation of the data was performed with Kaplan–Meier survival curves. Multivariate analysis was performed with a Cox proportional hazard model, with age, presence of bronchiectasis, use of inhaled colistin, azithromycin, and inhaled hypertonic saline, as the covariates. The proportionality assumption was checked with the Schoenfeld test.

Results

Fifty-four children with CSLD or bronchiectasis, and isolation of Pa in at least one clinical sample, were identified through the clinical records. The patient's clinical characteristics are shown in table 1. There were only 16 patients who had valid spirometries both at the time of Pa isolation and at the end of the follow-up period with no difference between the ppFEV1 values between the two time points (93.2±1.3, and 94.0±1.5, respectively, p= 0.43). The same comparison was also performed in the subgroup of 8 patients who attained remission and no difference was found (93.7±2.0, and 94.4±2.2, respectively, p= 0.68).

The Cox proportional hazards model showed that the use of nebulised colistin and the presence of bronchiectasis at HRCT scan were statistically significant predictors of remission (HR:3.99; 95%CI:1.12-14.14; p= 0.032, and HR:0.24; 95%CI:0.08-0.71; p= 0.010). The estimated HRs indicated that patients on colistin were, on average, approximately four times more likely to achieve remission compared to patients not treated with this drug whereas patients with radiologically confirmed bronchiectasis were, on average, approximately four times less likely to achieve remission compared with patients without bronchiectasis. Age, use of azithromycin, and hypertonic saline inhalation were also included as covariates in the Cox model but no significant correlation between them and remission was established (HR:1.13; 95%CI:0.99-1.28; p=0.06, HR:1.34; 95%CI:0.46-3.93; p= 0.58 , HR:0.80; 95%CI:0.22-2.87; p= 0.74, respectively). The differences in time to remission for the two significant predictors are shown in Figure 1.

The Schoenfeld tests showed that there was no violation of the proportional assumption in our model (all p >0.05).

Gender (M/F)
Median (IQR) age of wet cough onset (years)
Median (IQR) duration of wet cough before the isolation of Pa (years)

Median (IQR) duration of follow-up (years)	
Median (IQR) age of first Pa isolation (years)	
Patients with Pa isolation more than once	
Other isolated bacteria Pneumococcus Haemophilus influenzae Moraxella catarrhalis Staphylococcus aureus Gram-negative	
Children on long term inhaled colistin (n; %)	
Children on long term azithromycin (n;%)	
Children on long term nebulized hypertonic saline (n;%)	
ppFEV1 (IQR)*	
Children with radiologically confirmed bronchiectasis	
Median (IQR) modified Bhalla score**	

Pa: Pseudomonas aeruginosa IQR: Interquartile range Gram-negative: Pathogenic gram-negative bacteria (Enterobacteriace

Discussion

The absence of clear national or international guidelines for the eradication and suppression of Pa in children with non-CF chronic endobronchial infection resulted in a non-unanimous approach from the doctors serving in our department, with treatment decisions being based on the subjective clinical judgment of each physician. Nevertheless, the different therapeutic attitudes were an advantage for this retrospective study which aimed to explore the efficacy of different treatment modalities. The study showed that treatment with inhaled colistin increased whereas the presence of radiologically confirmed bronchiectasis reduced the rate of remission. Our data were unable to show any significant correlation between remission and the two other treatment modalities namely, azithromycin and inhaled hypertonic saline.

The presence of Pa in the airways of patients with non-CF bronchiectasis has been associated with accelerated lung function decline and increased morbidity and mortality[7,13,14]. However, despite the advantages in our knowledge of Pa bronchial infections, much of our understanding is still extrapolated from CF[15]. Furthermore, it is difficult to estimate the true impact of primary Pa infection in pediatric patients. Indeed, specific data on children are lacking and most of the available studies in adults have concentrated on chronic – and not primary - infection.

There is no universally accepted definition of chronic Pa infection with most of the currently used definitions being based on microbiological results from sputum cultures in CF patients[16]. However, young children rarely expectorate sputum and this fact dictates the use of alternative methods for microbiological sample collection. BAL is taken through an interventional procedure and cannot be used in the usual follow-up. Practically, cough and throat swabs are the only possible alternatives to sputum. These latter methods, however, despite being very convenient, place considerable uncertainty on the results as they lack the sensitivity of sputum or BAL cultures[17]. Furthermore, in cases of biofilm formation, it can be difficult to recover all the clinically significant bacteria through conventional cultures [18]. For the above reasons, the isolation of Pa for the first time cannot exclude the existence of a chronic Pa infection, especially if the symptoms persist for a long period and/or the child has repeatedly not responded in conventional antibiotics. The difficulty and ambiguity in characterizing a first-time Pa isolation as new onset or chronic infection can justify the use of inhaled antibiotics for prolonged periods.

Inhaled antibiotics deliver very high drug concentrations at the airways without the adverse effects that are observed when they are administered through systemic routes[19,20]. Although many inhaled antibiotics have been developed and are currently in use, only colistin was available for our patients since it is the only inhaled antibiotic that is compensated by the national health insurance system for non-CF patients. Long-term treatment with inhaled antibiotics reduces the number of exacerbations, decreases bacterial load, and improves pulmonary function in several chronic endobronchial infections[19,21-23]. Our data are in general agreement with the above results as they demonstrated that the prolonged use of inhaled colistin increased the rate of remission.

Bronchiectasis is the end stage of chronic endobronchial infections[2] and its presence is correlated with the severity of clinical symptoms and the intensity of neutrophilic inflammation in the airways[3]. As such it is inherently hard – though not impossible - to remit[10,24]. Given so, our finding that the presence of bronchiectasis reduces the rate of remission was somehow expected as bronchiectasis denotes the most severely affected patients.

The present study suffers from some limitations. First of all, it was a single-centre observational study that reflected the population served by our department, and the results cannot be generalized. The number of patients was relatively small and so type 2 errors (false-negative results) concerning treatment with azithromycin and nebulized hypertonic saline, may have occurred. Finally, we used a functional definition of remission which may not be equivalent to true remission.

In conclusion, inhaled colistin is a useful therapeutic modality in children with CSLD and non-CF bronchiectasis. Children with CSLD have a more favourable prognosis compared to children with established bronchiectasis.

Figure 1 : Persistence of the disease in patients with and without treatment with nebulized antibiotics (A), and presence or absence of bronchiectasis (B)

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