

Non-tuberculous mycobacteria in cystic fibrosis

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Abstract

Background—The clinical significance of the presence of non-tuberculous mycobacteria in the sputum of patients with cystic fibrosis is unclear. A retrospective case-control study was performed to assess possible risk factors for non-tuberculous mycobacteria and its impact on clinical status in patients with cystic fibrosis.

Methods—The records of all patients attending the Leeds cystic fibrosis clinics who were positive for non-tuberculous mycobacteria were examined. Each case was matched with two controls for sex, age, and respiratory function at the time of the first non-tuberculous mycobacteria isolate. Details of respiratory function, nutritional status, antibiotic and corticosteroid therapy, Shwachman-Kulczycki (S-K) score, Northern chest radiographic score, and the frequency of isolation of other bacteria and fungi were collected from two years before to two years after the first non-tuberculous mycobacteria isolate. The patients' genotype and the presence of diabetes mellitus were also recorded.

Results—Non-tuberculous mycobacteria were isolated from 14 patients out of a cystic fibrosis population of 372 (prevalence = 3.8%). No significant effect of non-tuberculous mycobacteria was seen on respiratory function, nutritional status, or S-K score. There was a significant association with the number of intravenous antibiotic courses received before the first isolate with cases receiving, on average, twice as many courses as controls (cases 6.64, controls 2.86, 95% CI for difference 1.7 to 5.9). No significant difference was seen between cases and controls for Northern scores, previous steroid therapy, or the incidence of diabetes mellitus.

Conclusions—Non-tuberculous mycobacteria infection in patients with cystic fibrosis is uncommon and its clinical impact appears to be minimal over a two year period. Frequent intravenous antibiotic usage is a possible risk factor for colonisation with non-tuberculous mycobacteria.

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ing incidence in both the UK and USA.^{1,2} This increase has occurred in both absolute numbers and as a proportion of all mycobacteria isolated, and is only partly explained by the emergence of HIV infection. There has been a simultaneous growing awareness of non-tuberculous mycobacteria in cystic fibrosis, with some studies highlighting their potential pathogenicity³⁻⁷ while others have failed to show any significant clinical effect on patients.^{8,9} With life expectancy in cystic fibrosis increasing and other bacterial infections being more effectively treated, it is likely that non-tuberculous mycobacteria will continue to be increasingly isolated from sputum. It is therefore important that their pathogenic role, if any, is better understood and that optimal management protocols are defined. Establishing the significance of non-tuberculous mycobacteria in an individual patient is difficult as symptoms and signs may be due to other concurrent respiratory infections, radiographic changes are non-specific, and a gradual deterioration in clinical status is part of the natural history of cystic fibrosis. Moreover, the non-tuberculous mycobacteria isolated may merely represent environmental contamination¹⁰ or simple colonisation of the airways.¹ Skin testing is unhelpful due to its low predictive value¹¹ and under-reporting of non-tuberculous mycobacteria infection may occur because of overgrowth of culture media by *Pseudomonas* species.^{6,7,12}

The aim of this study was to analyse retrospectively data in patients with cystic fibrosis from whom non-tuberculous mycobacteria were isolated, in an attempt to establish possible risk factors for infection and to assess its impact on clinical status.

Methods

The adult and paediatric cystic fibrosis units in Leeds, with populations of 229 and 143 respectively, have been screened routinely for non-tuberculous mycobacteria since 1989 (adults) and 1994 (children). Prior to this, examination of sputum for non-tuberculous mycobacteria was performed in individual patients when clinically indicated. Sputum is examined directly for acid-fast bacilli and cultured, following decontamination with 4% sodium hydroxide/2.5% oxalic acid solution, on Lowenstein-Jensen media.

The records of 14 patients with either single or multiple isolates of non-tuberculous mycobacteria over a seven year period were examined. Each case was matched with two controls for sex, age (± 2 years), and respiratory function ($\pm 20\%$) at the time of the first non-tuberculous mycobacteria isolate. Details of respiratory function, nutritional status, treatment received

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Pulmonary infection with non-tuberculous mycobacteria is known to be associated with chronic lung disease and impaired immunity,¹ and the last two decades have seen an increas-

Table 1 Characteristics of study patients

Case no.	Sex	Age (years)	Genotype	Diabetes	Smear +ve	Culture +ve	NTM type	Treatment
1	M	18	DF508/508	No	0	3	<i>M chelonae</i>	None
2	M	25	DF508/508	No	0	2	<i>M fortuitum</i>	None
3	M	16	DF508/508	Yes	6	4	<i>M avium</i>	None
4	F	17	DF508/508	No	0	3	complex	None
5	M	17	DF508/508	No	2	5	<i>M malmoense</i>	None
6	M	16	DF508/508	No	3	3	<i>M chelonae</i>	None
7	M	19	Unknown	No	0	1	<i>M fortuitum</i>	None
8	M	21	DF508/508	Yes	2	12	<i>M avium</i>	None
9	M	19	DF508/508	No	5	7	complex	Yes*
10	M	9	DF508?	No	5	6	<i>M fortuitum</i>	Yes†
11	F	10	DF508?	No	0	1	<i>M avium</i>	None
12	F	15	DF508/508	Yes	0	1	complex	None
13	F	9	G551D/G85E	Yes	0	1	<i>M fortuitum</i>	None
14	M	14	DF508/508	No	9	5	<i>M chelonae</i>	None
							<i>M fortuitum</i>	Yes‡

NTM=non-tuberculous mycobacteria.

*Rifabutin and ethambutol (18 months).

†Rifampicin, ethambutol and clarithromycin (21 months).

‡Rifampicin, ethambutol and clarithromycin (intermittent treatment over two years).

Table 2 Analysis of continuous variables

Continuous variable measured	Cases	Controls	Difference	Paired <i>t</i> test	<i>p</i> value	95% CI (for difference)
S-K score (mean change)	-8.18	-4.32	-3.86	-1.57	0.15	-9.4 to 1.6
N score (mean change)	4.08	1.88	2.21	2.06	0.06	-0.2 to 4.6
FEV ₁ (mean change)	-0.03	-0.21	0.17	0.48	0.65	-0.7 to 1.0
FVC (mean change)	0.22	0.18	0.04	0.09	0.93	-1.1 to 1.2
Nutritional status (mean change)	1.23	0.77	0.46	0.43	0.68	-2.0 to 2.9
Mean no. intravenous antibiotic courses	6.64	2.86	3.79	3.86	0.002	1.7 to 5.9

S-K score = Shwachman-Kulczycki score; N score = Northern radiographic score; FEV₁ = forced expiratory volume in one second; FVC = forced vital capacity.

Table 3 Analysis of dichotomous variables

Dichotomous variable	Status	Cases	Controls	Significance
Diabetes mellitus	Yes	4	4	$\chi^2 = 0.45, p = 0.5$
	No	10	24	
Nebulised antibiotics	Yes	10	19	$\chi^2 = 0.02, p = 0.89$
	No	4	9	
Steroid use	Yes	8	7	$\chi^2 = 3.13, p = 0.08$
	No	5	19	

(including nebulised antibiotics, number of intravenous antibiotic courses, and nebulised, inhaled or oral steroids), Shwachman-Kulczycki (S-K) score,¹³ and Northern (radiographic) score¹⁴ were collected two years before, at the time of the first non-tuberculous mycobacteria isolate, and two years thereafter. The frequency of isolation of other bacteria and fungi was also recorded, as were the patients' genotypes and whether or not they suffered from diabetes mellitus. Those cases who received treatment for non-tuberculous mycobacteria infection were noted. The nutritional status of the adults was calculated as body mass index (BMI) and that of the children as percentage weight/height. Respiratory function was measured as forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁) using a Vitalograph Compact II machine (Vitalograph Ltd, Buckingham, UK). For the continuous variables, statistical analysis was performed using the paired *t* test, the case values being compared with the average of the two control values. The dichotomous variables were analysed using a χ^2 test on matched sets with unequal outcomes.¹⁵

A subgroup of cases with multiple isolates of non-tuberculous mycobacteria was also analysed separately.

Results

Five different species of mycobacteria were isolated in 14 patients, with *M fortuitum*, *M avium* complex, and *M chelonae* occurring most commonly (table 1). The 14 cases comprised nine adults and five children, 4% and 3.5% of the respective clinic populations. The age range was 9–25 years with a median of 16 years. The median age of the paediatric clinic population is 11 years, and for the adult clinic 24 years. Eight of the nine adult cases were male compared with an adult clinic sex ratio of 52% female to 48% male.

Each case with its two controls constitutes a single set. Data on each of the variables assessed were complete for all sets apart from the following categories: steroid therapy (13 sets complete); Northern score (12 sets); respiratory function, nutritional status and S-K score (11 sets). Only those sets with complete data were subject to analysis. Follow up data on cases 1, 3, 6, and 13 were limited to 18 months.

Overall, no significant effect of non-tuberculous mycobacteria was seen on respiratory function, nutritional status, or S-K score (table 2). Cases tended to have worse Northern chest radiograph scores, although this did not achieve statistical significance ($p = 0.06$). There was no significant difference between cases and controls in the incidence of diabetes mellitus, genotype, frequency of other bacteria or fungi isolated, or in the use of nebulised antibiotic therapy (table 3). Cases had received significantly more intravenous antibiotic courses before the first isolate was identified ($p = 0.002$) and, although they were more likely to have received steroid therapy of any kind ($p = 0.08$), particularly if they were adults ($p = 0.06$), neither of these changes was statistically significant. There was no observable attributable effect in those individuals who received treatment for non-tuberculous mycobacteria (cases 9, 10, and 14). A subgroup analysis excluding sets 7, 11, 12, and 13 (which contain cases with a single mycobacterial isolate only) resulted in the same conclusions; the difference between cases and controls with respect to the number of intravenous antibiotic courses received before the isolate was identified was reduced but still significant ($p = 0.015$).

Discussion

Although initially discovered shortly after Koch identified the tubercle bacillus in 1882, non-tuberculous mycobacteria were not generally recognised as potentially pathogenic until the 1950s.¹⁶ More recently there have been reports of fatal non-tuberculous mycobacteria infection in cystic fibrosis^{3 17} and subsequent studies have cited prevalence rates for non-tuberculous mycobacteria ranging from 1.8% to 20% in cystic fibrosis populations.^{3 5–9 18} Differences in inclusion and diagnostic criteria, as well as the varying geographical distribution of environmental mycobacteria, lead to difficulties in making direct comparisons between

these reports. Some authors have seen patients improve with treatment for non-tuberculous mycobacteria,⁵ while others have failed to note any benefit.⁹ The issue is further complicated by the difficulties in distinguishing simple colonisation from infection, although the presence of at least two positive smears or cultures is recommended by the American Thoracic Society to establish a diagnosis of the latter.¹⁶ In a recent necropsy study, Tomaszefski *et al* found evidence of active mycobacterial disease in only two of six patients with cystic fibrosis who had had multiple positive sputum cultures, although interestingly only these same two cases had multiple positive smears for acid-fast bacilli.¹⁹ Twelve other patients with a single positive sputum culture had no evidence of mycobacterial pathology at necropsy.

Risk factors for pulmonary infection with non-tuberculous mycobacteria in the general population include chronic lung disease and immunosuppression.¹⁶ There is no evidence of any systemic immune defect in patients with cystic fibrosis²⁰ and interest has focused on determining other predisposing factors in this group. Aitken *et al* reported eight cases (from 64 adult patients with cystic fibrosis) who tended to be older and have lower clinical scores, but found no association with radiographic findings, diabetes mellitus, respiratory function, or genotype.⁸ Kilby *et al* found that adult patients with non-tuberculous mycobacteria were similar to those without, although cases again tended to be older. In addition, they noted no association with the presence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, or *Aspergillus* species in the sputum.⁷ Hjelte *et al* reported five cases (aged 11–25 years) from a cystic fibrosis population of 54 and did not observe any association with corticosteroid usage, diabetes, or poor nutritional state.⁵ All five patients had progressive radiographic shadowing and deteriorating lung function at the time of positive sputum cultures and all five improved with specific chemotherapy. However, one of these cases had persistently negative smears and one positive culture yielding *M. gordonae*, which is rarely pathogenic. More recently, Fauroux *et al* reported two teenage patients with severe lung disease from a cystic fibrosis population of 106 who had positive smears and sputum cultures for *M. chelonae*.¹⁸ Both were treated with clarithromycin with subsequent clearance of the non-tuberculous mycobacteria from the sputum. However, clinical and functional status continued to decline in one, and the other saw only an initial improvement which may have been temporary. Apart from the possibility that the non-tuberculous mycobacteria were not related to the clinical status, these cases highlight the fact that clearance of non-tuberculous mycobacteria from sputum in those with suspected infection does not necessarily indicate cure, and that claims of successful treatment may be premature. In this regard, Heurlin and Petrini have reported 25 cases of non-tuberculous mycobacteria infection in patients without AIDS, 22 of whom received chemotherapy.²¹ After more than two years follow up, following the

completion of chemotherapy, only seven appeared to be free of disease.

In our study there was only a slight increase in the prevalence of non-tuberculous mycobacteria isolated from the adult cystic fibrosis population when compared with the children, but the child cases were all aged nine years or older. There was a male preponderance in the adult cases that was not reflected in the background population. Overall, cases tended to have worse Northern chest radiographic scores and were more likely to have received corticosteroids than controls, but neither of these changes reached statistical significance. This may reflect the small sample size and resultant low study power. Cases had also received significantly more courses of intravenous antibiotics. This latter association may simply be a surrogate marker for progressive lung damage, predisposing to infection with non-tuberculous mycobacteria, although we did not observe a parallel significant deterioration in respiratory function or S-K score. Alternatively, it may be a true effect by way of repeatedly altering the bacterial flora of the airways, permitting colonisation with non-tuberculous mycobacteria and subsequent infection. A third possibility is that a delay in recognition of non-tuberculous mycobacteria infection leads to prolonged courses of intravenous antibiotics for presumed bacterial infection. We did not note any association with diabetes mellitus, genotype, nutritional status, or the frequency of other bacteria or fungi isolated. The three cases who received treatment for non-tuberculous mycobacteria (cases 9, 10, and 14) did so because of clinical deterioration despite antibacterial and antifungal treatment. Case 10 showed some initial improvement, but this was not uniformly sustained over the treatment course. Cases 9 and 14 did not appear to benefit from non-tuberculous mycobacterial treatment, although there was poor compliance with therapy in case 14. There has been no significant attributable deterioration in those cases with multiple positive smears and sputum cultures who did not receive treatment for non-tuberculous mycobacteria (cases 3, 5, 6, and 8). There were not enough data on skin testing to warrant analysis. Others have found its predictive value to be low in patients with cystic fibrosis because of the high prevalence of cross reactivity between mycobacterial species and the problem of anergy in patients with advanced disease.¹¹

This study is limited by its small size and retrospective nature. However, it does indicate that the overall prevalence of non-tuberculous mycobacteria in patients with cystic fibrosis is low and that the clinical impact is likely to be minimal in most individuals over a two year period. The possible link with frequent intravenous antibiotic usage and steroid therapy warrants further investigation and can only be clarified by a large, multicentre, prospective trial. Such a trial would not only help to define significant risk factors for non-tuberculous mycobacteria infection in cystic fibrosis but would also help in producing guidelines for diagnosis and identification of

those patients who would benefit most from chemotherapy.

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