Risk factors for non-tuberculous mycobacterial pulmonary disease (NTM-PD) in Croatia

ABSTRACT

Background: The incidence, geographical distribution and clinical relevance of different non tuberculous mycobacteria (NTM) in Croatia is well described. There are few data on the risk factors for developing NTM pulmonary disease (NTM-PD) in our setting.

Methods: We conducted a retrospective cohort study on all Croatian residents with NTM isolated from respiratory samples in the period from 2006 to 2015 with follow up to 2018. ATS/IDSA guidelines were used to establish NTM-PD diagnosis. Clinical, radiological and treatment data were collected from hospital records.

Results: Risk analysis calculations were made on the 439 isolation episodes that were classified as definitive NTM-PD (n=137) or no disease (n=302). Female gender, presence of bronchiectasis, low BMI and long term systemic corticosteroid therapy were independent risk factors associated with NTM-PD. Hemoptysis and malaise were presenting symptoms independently associated with NTM-PD. COPD and low/moderate dose inhaled corticosteroid (ICS) therapy were not associated with NTM-PD. High dose ICS therapy was a significant risk factor for developing NTM-PD (aOR=4.73, CI 1.69-13.23 p=0.003).

Conclusions: NTM-PD patients in Croatia are similar to those in other published cohorts in terms of their characteristics and risk factors. The significant, dose-dependent, association between ICS use and NTM-PD add to the body of evidence suggesting that high dose ICS use is associated with NTM-PD.

Keywords: non tuberculous mycobacteria, NTM-PD, risk factors, patient characteristics

INTRODUCTION

Pulmonary disease caused by non-tuberculous mycobacteria (NTM-PD) is increasingly recognized as an important clinical entity in humans [1-3]. The diagnosis of NTM-PD is complex and treatment requires long-term administration of species-specific multidrug regimens [4].

NTM-PD most often occurs in elderly patients with or without underlying lung disease. Patients with underlying lung disease such as chronic obstructive lung disease (COPD) usually present with cavitary disease. In contrast, patients without previous lung disease are usually non-smoking women who present with the nodular bronchiectatic form of NTM-PD [5].

The most important known risk factors for developing NTM-PD are chronic lung disease and immunological disorders. Patients suffering from chronic lung diseases such as cystic fibrosis (CF), bronchiectasis and pneumoconiosis all have significantly increased risk for developing NTM-PD. Organ transplant recipients, patients with AIDS and patients receiving anti-TNFα agents usually present with disseminated NTM disease, with several papers reporting severe isolated NTM-PD [5-8].

Our previous studies showed that distribution of NTM species and NTM-PD incidence in Croatia varies according to geographical region, with higher incidence of NTM-PD in the coastal as compared to the continental region. In our setting, NTM species differed in clinical relevance, with *Mycobacterium xenopi* and *Mycobacterium avium* complex (MAC) being the most frequent causative agents of NTM-PD [9,10].

In this study we aimed to determine the risk factors leading to the development of NTM-PD in Croatian patients.

PATIENTS AND METHODS

We conducted a retrospective cohort study on all Croatian residents with NTM isolated from respiratory samples in the period from January 1st 2006 to December 31st 2015, with follow up to December 31st 2018. Information on all isolated species and patient information was obtained from the National Reference Mycobacteria Laboratory (NRML) at the Croatian Institute of Public Health (CIPH). All NTM species were identified by molecular methods (GenoType® CM/AS; Hain Lifescience GmbH). Clinical, radiological and treatment data were collected using the available patient information and hospital records across the whole country. An isolation episode was defined as one or more NTM isolates from a single person. ATS/IDSA guidelines were used to establish NTM-PD diagnosis [4]. Patients with concomitant active tuberculosis were excluded from the analysis. The differentiation between nodular-bronchiectatic (NB) and cavitary disease was made based on radiologist reports from the available radiographic (chest X-ray and/or CT scan) images. Among patients with concomitant diagnosis of chronic obstructive pulmonary disease (COPD) or asthma and known usage of inhaled corticosteroid therapy (ICS), stratification according to the daily ICS dose was made. High dose of ICS was defined as >1000 beclometasone dipropionate (BDP) equivalent per day. Microsoft Excel (Microsoft, Redmond, WA, USA) was used to tabulate data, calculate frequencies, percentages and median ages. The $\chi 2$, Fischer's exact and t-tests were calculated using MedCalc (MedCalc Software, Ostend, Belgium). Multivariable logistic regression modelling included non-overlapping factors that were found to be significant in the univariate analysis. An additional model to assess ICS association with NTM-PD was performed on a subset of 191 patients with full treatment data and known ICS dose. The model included the same, aforementioned factors that were found to be significant in the univariate analysis.

The study was approved by the Ethics Committee of the Croatian Institute of Public Health (file number 001-487/1-10).

RESULTS

A total of 1926 NTM isolates were identified from 1875 patients. The distribution of NTM isolates according to the species is shown in Table 1. Complete medical records were available for 468 (24.3%) of all NTM isolates. The most commonly encountered NTM species was *M. gordonae*, a saprophyte NTM species that rarely causes pulmonary disease. Complete medical records with clinical and radiological information were available in a smaller proportion of cases of *M. gordonae*, as well as some other non-pathogenic species, but significantly higher in case of clinically relevant NTM species (Table 1).

Subsequent risk analysis calculations were based on the 439 isolation episodes that were either classified as definitive NTM-PD (n=137) or no disease (n=302).

In our NTM-PD cohort, the mean age was 66.5 (vs 66 in the group without NTM-PD). Males predominated in both groups (52.6% in the NTM-PD group and 66.2% in the no disease group). The characteristics of the patients in our cohort are shown in Table 2.

There was a small number of patients with systemic immunosuppression in our cohort: 2 cases of HIV in the NTM-PD group and 3 in the no disease group, 1 patient with common variable immune deficiency (CVID) in the NTM-PD group and 2 solid organ transplant recipients in the NTM-PD group with 1 transplant recipient in the no disease group. A total of 5 patients in each group received systemic immunosuppressive therapy other than corticosteroids: 1 patient was treated with mycophenolate mofetil and everolimus, 4 patients with azathioprine, and 2 patients with tacrolimus and methotrexate each. There were no patients treated with anti-TNFα agents in our cohort. Both CF patients included in our cohort had NTM-PD.

Among cases of definite NTM-PD, fibro-cavitary (FC) and nodular-bronchiectatic (NB) radiological forms were present in 38 (27.7%) and 89 (65%) of all NTM-PD cases, respectively. The remaining 10 (7.3%) had a different radiological presentation such as a tumor like infiltrate or pleural effusion. 49 (35.8%) patients with NTM-PD were acid-fast bacilli (AFB) positive at the time of diagnosis, while only 7 patients in the no disease group had an AFB positive sputum. Both FC and NB radiological NTM-PD forms were equally represented in the subgroup of patients with AFB positive NTM-PD.

In the unadjusted analysis, patients with NTM-PD were more likely to have bronchiectasis, a prior history of NTM-PD, prior history of TB, rheumatological disorder (RD), a low body mass index, and a history of long-term systemic steroid therapy. Interestingly, COPD was not

associated with NTM-PD. Presenting signs and symptoms associated with NTM-PD in the unadjusted analysis included hemoptysis, productive cough, appetite loss and malaise.

Within the sub-group of patients with COPD and/or asthma (n=208), usage of inhaled corticosteroid therapy (ICS) was evaluated in those with full treatment data available (n=191) (shown in Table 3). After adjusting for the same factors that were associated with NTM-PD in the univariate analysis, high dose ICS therapy was significantly associated with NTM-PD, while we found no association between low/moderate ICS therapy and the disease. Gender, presence of bronchiectasis, low BMI, long term systemic corticosteroid therapy, hemoptysis and malaise were retained as significant in both multivariate models (shown in Table 2).

All of the patients treated with high dose ICS (N=73) therapy received high dose fluticasone (>500 mcg). In the low/medium dose group patients were treated with budesonide (N=14; 3 in the NTM-PD group, 11 in the no disease group), medium dose fluticasone (250-500 mcg; N=13; 7 in the NTM-PD group, 6 in the no disease group), ciclesonide (N=3; 1 in the NTM-PD group, 2 in the no disease group) and beclomethasone (N=1, in the no disase group). Medium dose fluticasone was not significantly associated with NTM-PD when compared to medium dose budesonide (OR=4.28, 95% CI 0.79-22.92, p=0.089).

DISCUSSION

In this study we found that female gender, presence of bronchiectasis, low BMI, long term systemic corticosteroid therapy, high dose ICS therapy and presentation with hemoptysis and malaise were more prevalent among patients with NTM-PD according to the current diagnostic criteria [4] than among patients with NTM isolates but no evidence of disease. These may thus be risk factors for development of NTM-PD. High dose ICS therapy was strongly associated with NTM-PD.

NTM were more frequently isolated in men (1112 isolation episodes vs. 814 isolation episodes in women) and males predominated in both the NTM-PD and the no disease group, but female sex was shown to be an independent risk factor for NTM-PD in the subsequent analysis. The relative distribution of NTM species is similar in both sexes. We hypothesize that the increased isolation frequency in men is most likely due to more frequent routine sputum sampling and pulmonary follow up for other respiratory diseases which are more prevalent among men than women in Croatia (i.e. COPD, lung cancer etc.) [11].

The observation that female sex is an independent risk factor for NTM-PD is in accordance with several published studies [5,12,13]. The frequently cited voluntary cough suppression hypothesis as a risk factor in women (Lady Windermere syndrome) is still unproven [14]. A protective role of estrogen in the pathogenesis of NTM-PD was confirmed in a mouse model, suggesting that lower levels of estrogen in postmenopausal women could be a risk factor for developing NTM-PD [12,15,16]. Possible molecular mechanisms underlying estrogen mediated protection include enhancement of macrophage phagocytic function, increased macrophage Fcγ receptor expression and enhanced macrophage production of reactive nitrogen species [15,17,18].

A low body mass index (BMI) was significantly associated with NTM-PD in our cohort. As hypothesized by several studies, altered expression of leptin and adiponectin in patients with low BMI might increase the risk of mycobacterial infection [12,19]. Bronchiectasis, too, is a well described risk factor (and important consequence) for NTM-PD, and this association was confirmed in our cohort. Interestingly, there was a very small number of patients with systemic immunosuppression in our cohort and they were thus excluded from further analysis. Immunocompromised patients primarily present with disseminated NTM disease, not NTM-PD, which is the main focus of our research [5].

In the unadjusted analysis COPD was not associated with NTM-PD (OR 1.14, p=0.535). This finding contrasts with the findings of a study done on the Danish population (OR 2.15,

p<0.0001), but is similar to the findings from a Belgian retrospective analysis (OR 1.00) [3,20]. Even though it is known that obstructive lung diseases (OLD), such as asthma and COPD, are risk factors for NTM-PD, it is unclear whether the association between NTM-PD and OLD is due to structural and/or functional abnormalities, medications used in the treatment of OLD, combination of these factors or some other factors. The two studies examining the impact of ICS use in patients with OLD showed ICS treatment to be a strong risk factor for NTM-PD [21,22]. Both studies also found that the association between ICS use and NTM-PD is dose-dependent, i.e. high dose ICS yields a higher risk than low-dose ICS use. This association is unlikely confounded by severity of OLD [22]. Data from our study add to that body of evidence, suggesting that high dose ICS use is an independent risk factor for developing NTM-PD.

Although direct comparison is difficult due to different study design, our estimate of NTM-PD risk in patients on high dose ICS (aOR 4.73) is comparable to that from the Danish cohort (aOR 3.8) while it is somewhat higher than in the Ontario cohort (aOR 2.28).

The association between ICS use and NTM-PD is also dependent on the medical compound. Data from both aforementioned studies suggests that use of fluticasone represents a higher risk for NTM-PD than other types of ICS (i.e. budesonide) [21,22]. Since all of the patients using high dose ICS included in our study were using high dose fluticasone (>500 mcg) it is difficult to determine whether the association found between NTM-PD and high dose ICS is dependent only on the dose of ICS, only on the compound, or both factors contribute equally to the increased risk of NTM-PD in this subgroup. When comparing medium dose budesonide with medium dose fluticasone there was a trend towards, but no statistically significant association between fluticasone and NTM-PD (OR=4.28, 95% CI 0.79-22.92, p=0.089), which is most likely due to the small number of patients in both groups. The predominance of high dose fluticasone in our cohort is most likely a consequence of the study period during which fluticasone 500 mcg twice daily, especially in combination with salmeterol 50mcg, was one of the main treatment options for patients with COPD [23].

Main limitations of our study are its retrospective nature and incomplete medical records for a significant proportion of isolation events. However this is mainly due to the fact that most patients with isolated NTM species of low clinical relevance were not referred for full medical checkup. In fact, for the clinically most relevant species in our setting [10], the coverage amounted to over 50%, as shown in table 1. A relatively small absolute number of

patients with OLD and lack of comprehensive data on the severity of OLD disenabled more detailed assessment of association between OLD and NTM-PD.

In conclusion, NTM-PD patients in Croatia are similar to those in other published cohorts in terms of their characteristics and risk factors. The significant, dose-dependent association between ICS use and NTM-PD add to the body of evidence suggesting that ICS use, especially high dose ICS, is associated with NTM-PD and it should be prescribed with caution.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics standards statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008

The study was approved by the Ethics Committee of the Croatian Institute of Public Health (file number 001-487/1-10).

Informed consent was obtained from all patients for being included in the study.

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Table 1. Frequency of isolation of nontuberculous mycobacteria (NTM) and NTM pulmonary disease (NTM-PD) in Croatia.

NTM	Total n (%)	Gender		Medical records evaluated (%)[a]	ATS/IDSA NTM-PD diagnostic criteria[b]		
		M n (%)	F n (%)		Definite disease (%)	Probable disease (%)	No disease (%)
M. gordonae	821 (42.6)	477 (42.9)	344 (42.3)	91 (11.1)	2 (2.2)	1 (1.1)	88 (96.7)
M. xenopi	294 (15.3)	188 (16.9)	106 (13)	165 (56.1)	54 (32.7)	17 (10.3)	94 (57)
M. fortuitum	220 (11.4)	138 (12.4)	82 (10.1)	57 (25.9)	2 (3.5)	0 (0)	55 (96.5)
M. terrae	128 (6.6)	67 (6.0)	61 (7.5)	7 (5.5)	0 (0)	0 (0)	7 (100)
MAC [e]	125 (6.5)	61 (5.5)	64 (7.9)	77 (61.6)	53 (68.8)	6 (7.8)	18 (23.4)
M. avium	71 (3.8)	34 (3.1)	37 (4.5)	43 (60.6)	31 (72.1)	3 (7)	9 (20.9)
M. intracellulare	45 (2.3)	22 (2)	23 (2.8)	28 (62.2)	20 (67.4)	0 (0)	8 (32.6)
M. chimaera [d]	6 (0.3)	5 (0.41)	1 (0.1)	5 (83.3)	2 (40)	2 (40)	1 (20)
MAC-undetermined	3 (0.1)	0 (0)	3 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)
M. chelonae	96 (5.0)	51 (4.6)	45 (5.5)	15 (15.6)	0 (0)	1 (2.3)	14 (97.7)
M. abscessus	41 (2.1)	21 (2)	20 (2.5)	12 (29.3)	6 (50)	1 (8.3)	5 (41.7)
M. kansasii	25 (1.3)	15 (1.3)	10 (1.2)	15 (60)	8 (53.4)	2 (13.3)	5 (33.3)
Other[c]	176 (9.1)	94 (8.4)	82 (10)	29 (16.5)	12 (41.4)	1 (3.4)	16 (55.2)
Total	1926 (100)	1112 (100)	814 (100)	468 (24.3)	137 (29,3)	29 (6.2)	302 (64.5)

[a] percentages reffer to row total; [b] percentages reffer to row total of evaluated medical records; ATS/IDSA – American Thoracic Society/Infectious Diseases Society of America,

[c] Two patients had co-infection with two different NTM species – one with *M. avium* and M. *xenopi* and other with *M. xenopi* + *M. kansasii*

[d] Identification of *M. chimaera* was available only for 23 *M. intracellulare* isolates from the year 2013 till the end of study period.

[e] MAC – *Mycobacterium avium* complex

Table 2. Characteristics of patients with definite nontuberculous mycobacteria pulmonary disease (NTM-PD) compared with patients without the disease.

Characteristics	Definite NTM-PD (n=137)	No disease (n=302)	OR (95 CI), p value	aOR (95 CI), p value
Demographics:				
Age (median. range)	66 (16-90)	66 (11-90)	0.99 (0.99 -1.01) P=0.8466	-
Female gender	65 (47.5%)	102 (33.8%)	1.77 (1.17-2.67) p=0.0065	2.27 (1.35-3.81) p=0.0019
Concurrent and predisposing conditions: n (%)				
COPD	62 (45.3)	127 (42.1)	1.14 (0.76-1.70) p=0.53	-
Asthma	3 (2.2)	17 (5.6)	0.375 (0.10-1.30) p= 0.122	-
Bronchiectasis	40 (29.2)	25 (8.3)	4.57 (2.63-7.93) p<0.0001	3.13 (1.59-6.18) p=0.001
Prior NTM-PD	7 (5.1)	1 (0.3)	16.21 (1.97-133.1) p=0.002	9.69 (0.9-103.81) p=0.061
Prior tuberculosis	38 (27.7)	58 (19.2)	1.62 (1.01-2.59) p=0.047	1.38 (0.77-2.49) p=0.282
Diabetes mellitus	18 (13.1)	42 (13.9)	0.936 (0.51-1.69) p=0.828	-
GERD	5 (3.6)	15 (5)	0.72 (0.26-2.06) P=0.54	-
Rheumatological Disease (RD)	9 (6.6)	6 (2)	3.47 (1.21-9.95) p=0.021	1.79 (0.47- 6.92) p=0.3933
Alcohol abuse	8 (5.8)	18 (6)	0.97 (0.41-2.31) p=0.96	-
BMI <18.5 kg/m^2	45 (32.8)	14 (4.6)	10.06 (5.28-19.16) p<0.0001	10.67 (5.07-22.43) p<0.0001
Systemic corticosteroid therapy	11 (8)	9 (3)	2.84 (1.15-7.03) p=0.026	3.3 (1.05-10.42) p=0.0416
Signs and symptoms				
Productive cough	104 (75.9)	189 (62.6)	1.88 (1.19-2.97) p=0.0064	1.67 (0.96-2.91) p=0.0669
Malaise	77 (56.2)	75 (24.8)	3.88 (2.53-5.95) p<0.0001	3.57 (2.09-6.07) P<0.0001
Appetite loss	47 (34.3)	64 (21.2)	1.94 (1.24-3.04) p=0.004	0.7 (0.38-1.29) p=0.2563
Fever	44 (32.1)	89 (29.5)	1.13 (0.73-1.75) p=0.577	-
Hemoptysis	34 (24.8)	29 (9.6)	3.10 (1.80-5.35) p<0.0001	3.55 (1.82-6.90) p=0.0002
Increased sweating	12 (8.8)	13 (4.3)	2.13 (0.94-4.80) p=0.067	-

Table 3. Use of ICS (inhaled corticosteroids) in patients with nontuberculous mycobacteria pulmonary disease (NTM-PD) compared with patients without the disease. ICS therapy was evaluated in 191 patients suffering from COPD or Asthma with full treatment data available

	NTM-PD (n=60) N (%)	No disease (n=131) N (%)	OR (95% CI), p value	aOR [b] (95 CI), p value
No ICS therapy	18 (30.0)	69 (52.7)	1	1
Low/medium dose ICS therapy[a]	11 (18.3)	20 (15.3)	1.25 (0.55- 2.80) p=0.673	1.86 (0.53-6.59) p=0.335
High dose ICS therapy	31 (51.7)	42 (32.0)	2.27 (1.21-4.23) p=0.011	4.73 (1.69-13.23) p=0.003

[a] There was a single patient in the No disease group with low dose ICS therapy

[b] Adjusted for the covariates: below normal BMI (<18.5 kg/m^2), bronchiectasis, prior NTM-PD, prior tuberculosis, systemic corticosteroid therapy, gender, rheumatic disease, hemoptysis, malaise, productive cough, appetite loss