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Non-tuberculous mycobacterial pulmonary disease: an Italian National survey

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Abstract. The incidence of non-tuberculous mycobacteria (NTM) infection is increasing in Europe. However, a picture of Italian epidemiology and clinical practice is missing. We performed a national Italian survey involving 42 respiratory medicine departments. The NTM species more frequently isolated were *Mycobacterium avium complex*, followed by *M. xenopi* and *M. kansasii*. Patients with NTM were more frequently female (57%), and over 60 years of age, with bronchiectasis and COPD as main comorbidities. Bronchoscopic samples were widely used in the diagnostic phase. Of all patients with NTM, 73% met the criteria for NTM pulmonary disease. Despite strong adherence to the guidelines, physicians found significant difficulties related to pharmacological adverse events, patients' compliance and poor outcomes. *(Sarcoidosis Vasc Diffuse Lung Dis 2018; 35: 21-25)*

Key words: non-tuberculous mycobacterial pulmonary disease, epidemiology, survey

Introduction

Non-tuberculous mycobacteria (NTM) are ubiquitous environmental organisms that comprehend more than 150 species and in susceptible patients may cause NTM pulmonary disease (NTM-PD). The diagnosis of NTM-PD is based on clinical, radiographic and microbiological criteria as suggested by the American Thoracic Society (ATS) guidelines in 2007 (1). However, the differentiation between lung colonisation and NTM-PD can be tough. Furthermore, population-based data have documented a continued increase in NTM prevalence in Europe and Italy in the last decades (2-4).

Despite an increase in the number of NTM isolations, an appropriate diagnostic and therapeutic evaluation is still challenging, and a real-life assessment of clinical practice in Italian respiratory medicine departments is needed.

With the support of AIPO (Associazione Italiana Pneumologi Ospedalieri - Italian Society of Hospital Pulmunologists), we conducted a national survey to collect data on NTM epidemiology and clinical practice of italian pulmunologists in regards to NTM-PD.

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Material and methods

The items in the questionnaire concerned all NTM isolations in non-Cystic Fibrosis (CF) patients in the 12 months prior to the receiving of the survey. The questionnaire was implemented by a committee of pulmunologists with expertise in respiratory infections (for the complete Questionnaire see Appendix 1).

An email from AIPO with link to the SurveyMonkey electronic questionnaire was sent on November 14th, 2016 to 436 respiratory medicine services, regardless of the volume of patients assisted and expertise in treating NTM patients, equally distributed between Northern (243 centers) and Southern Italy (193 centers) (the list of the respiratory services is available in Appendix 2), and remained active for four months.

The survey was classified as a service evaluation and formal ethical approval was not sought.

Results

Forty-two Respiratory Medicine Units responded to the questionnaire (10% response rate), 24 in Northern and 18 in Southern Italy (for complete collaborators list see the Acknowledgements). Response rate was equally distributed between Northern and Southern Italy (10% and 9%, respectively), Figure 1. The Units were subdivided as follows: 30 Respiratory Medicine Units with respiratory endoscopy service, 5 Respiratory Medicine wards without respiratory endoscopy service, 7 Respiratory Medicine outpatients clinics.

In regards to the availability of microbiological facilities 59% of centers reported to have a dedicated microbiology laboratory at their Institution to perform acid fast bacilli (AFB) typing, while 38% sent the sample to another microbiological laboratory for AFB typing.

The 42 Units who responded the questionnaire reported a total of 220 NTM isolations in the prior 12 months with a majority of centers (47%) who reported less than 6 NTM isolations, 37% who reported between 6 and 20 isolates and a minority (16%) who reported more that 20 isolates in the prior year.

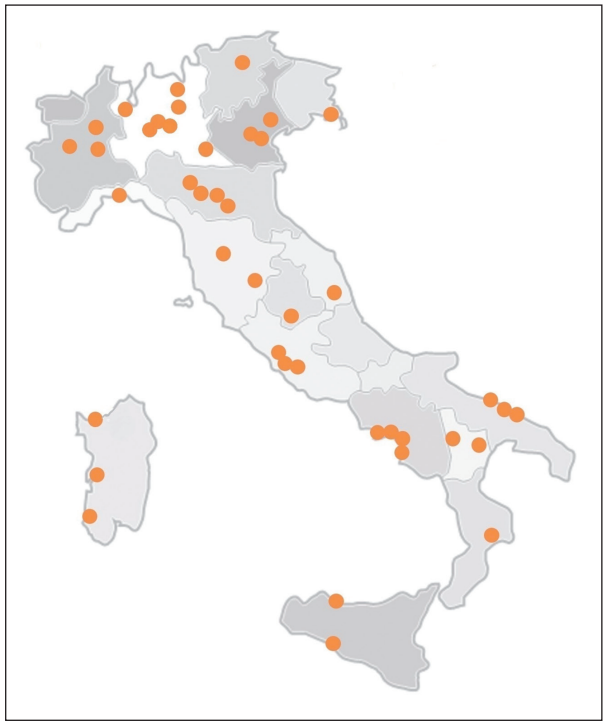

Fig. 1. Geographic location of respiratory medicine centers responding to the survey

NTM epidemiology and patients characteristics

Patients with NTM isolations were more frequently female (57%), and over 60 years of age (52% among women and 78% among men). Among the comorbidities reported, the most common were bronchiectasis (49% of patients) and chronic obstructive pulmonary disease (COPD) (35%), while a minority of cases showed prior tuberculosis infection (8%), other concomitant pulmonary infections (5%), lung cancer (3%), and asthma (1%).

In regards to the microbiological samples, the majority of centers reported to have isolated NTM species on sputum, bronchial aspirate and bronchoalveolar lavage. While, a minority reported to have isolated NTM species at least once on lung biopsies and lymphonode transbronchial needle aspiration (30% and 54%, respectively).

The most frequently isolated NTM species were MAC, followed by *M. xenopi, M. kansasii, M. abscessus* and *M. chelonae.*

Table 1. Percentage of patients who received antibiotic prescription according to the NTM species isolated

	M. avium complex	*M. kansasii*	*M. xenopi*
Azithromycin	65%	17%	22%
Clarithromycin	35%	17%	56%
Ethambutol	82%	83%	78%
Rifabutin	12%	0%	0%
Rifampicin	65%	67%	78%
Amikacin	29%	0%	22%
Isoniazid	0%	67%	33%
Ciprofloxacin	6%	0%	0%
Moxifloxacin	12%	33%	11%
Levofloxacin	6%	17%	22%

pNTM disease diagnosis and treatment

In regards to the diagnosis of NTM-PD, the majority of centers (88%) followed the criteria proposed by the 2007 ATS guidelines, while a minority of centers followed local guidelines or Ministry of Health and World Health Organization procedures. However, of all the NTM isolated, only 73% were considered to be clinically significant and to meet the criteria for NTM-PD according to the physician in charge. Most centers prescribed antibiotic treatment following the 2007 ATS guidelines as summarised in Table 1. Concomitant therapies included bronchodilation (prescribed by 81% of centers), respiratory physiotherapy (in 78% of centers), and mucolitics (in 54% of centers).

Most respiratory medicine specialists encountered problems with adverse events related to treatment and patients' compliance (56% and 37% of centers, respectively), 6% encountered problems in the diagnostic phase due to microbiological facilities availability.

Patients' outcomes and follow-up

In patients treated for NTM-PD, treatment success (respiratory specimens conversion without NTM infection recurrency) was achieved in 68% of patients, 20% had respiratory specimens conversion followed by relapse or new NTM infection, and 12% had NTM isolation persistence without respiratory specimens conversion.

Discussion

This is the first national survey to report current clinical practice on NTM-PD in Italian respiratory medicine departments and to shed light over some critical points.

First of all, the major problems encountered by physicians included adverse events related to treatment and patients' compliance, indicating that NTM-PD management still need to be improved. In particular, considering the non-optimal outcomes reported both in our and previous studies (5, 7), more importance should be given to adjuvant therapies that may favor pathogen eradication and prevention of recurrences. Bronchodilation and respiratory physiotherapy were the concomitant therapies most frequently prescribed in our survey, however, there are still no clear indications in regards to these treatments in NTM-PD guidelines.

Secondly, although microbiological testing availability was not considered by responding physicians as the major problem in NTM-PD management, more than 40% of centers reported not having microbiological availability for AFB typing at their Institution.

Our data on NTM epidemiology confirm a predominance of MAC, followed by *M. xenopi* and *M. kansasii*, showing similarities to other Italian cohorts such as those reported by Rindi et al. and Mencarini et al. (3, 4).

Future studies should include large prospective national databases to better evaluate epidemiology and clinical significance of NTM isolations.

Conclusions

Although great improvements have been made in the diagnostic phase thanks to the wide availability of endoscopic techniques, access to microbiology laboratories can still be ameliorate. In regards to treatment, despite strong adherence to the guidelines, physicians found significant difficulties related to adverse events, patients' compliance and poor outcomes.

Author Contributions:
Study concept and design: B.D.P., A.M.A, B.C., P.A.M., R.P., and P.F.; acquisition of data: B.D.P., A.M.A, B.C., P.A.M., R.P., and P.F.; analysis and interpretation of data: B.D.P., A.M.A, B.C., P.A.M., R.P., A.S., F.D.G., and P.F.; drafting of the manuscript: B.D.P., P.F., A.S., F.D.G.; critical revision of the manuscript for important intellectual content: all authors; study supervision: B.D.P., A.M.A, B.C., P.A.M., R.P., and P.F.; and read and approved the final manuscript: all authors.

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