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 Vasculit VS 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 Pulmonologists), we conducted a national survey to collect data on NTM epidemiology and clinical practice of Italian pulmonologists in regards to NTM-PD.
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 Survey-Monkey 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.

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 lymphnode 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.
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, 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 \textit{M. xenopi} and \textit{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.

**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%       |
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Identification of Center

First Name, Last Name:
Department:
City:

Center information

1) In how many patients referred to your Center have NTM been isolated in the last 12 months?
   0
   1-5
   6-10
   11-15
   16-20
   >20

Do you have a dedicated microbiology laboratory exist at your Institution?
   Yes
   No
   If yes, indicate laboratory’s name: _________________

2) Does the microbiology laboratory at your Institution perform acid fast bacilli (AFB) typing?
   Yes
   No, but AFB typing is performed in another Center
   No, AFB typing is not performed

3) If you answered yes to the prior question:
   Which method and kit are used (to be completed after sharing with the microbiologist):
   _________________
   Number of NTM isolated in the last 12 months: _________________

4) In which microbiological sample has the NTM been isolated? (indicate, if known, also the % of the total number of isolations)

| Sample   | Yes/No | % |
|----------|--------|---|
| Sputum   |        |   |
Questionnaire on Non-Tuberculous Mycobacterial (NTM) Pulmonary Disease in non-Cystic Fibrosis patients

| Procedure                                      | Yes/No | N. |
|------------------------------------------------|--------|----|
| Bronchial aspirate                             |        |    |
| Lung biopsy                                    |        |    |
| Lymphonode biopsy/transbronchial needle aspiration (TBNA) |        |    |
| Bronchoalveolar Lavage (BAL)                   |        |    |

Other (please specify): _________________

5) Which NTM have been isolated? (If known, also indicate the number of diagnosis)

| Mycobacterium avium complex                      | Yes/No | N. |
|-------------------------------------------------|--------|----|
| Mycobacterium Kansasi                           |        |    |
| Mycobacterium Xenopii                           |        |    |
| Mycobacterium Abscessus                         |        |    |
| Mycobacterium Chelonae                          |        |    |

Other (please specify): _________________

Features of patients in whom NTM have been isolated

6a) Gender

Male (%): _________________
Female (%): _________________

6a.i) Indicate, if known, the % of the total number of female patients per age group:

< 20-year-old (%): _________________
20-40-year-old (%): _________________
40-60-year-old (%): _________________
>60-year-old (%): _________________
6a.ii) Indicate, if known, the % of the total number of male patients per age group:

- < 20-year-old (%): _________________
- 20-40-year-old (%): _________________
- 40-60-year-old (%): _________________
- >60-year-old (%): _________________

6b) Smoking history (indicate the % of the total number of patients)

- Smokers (%): _________________
- Never smokers (%): _________________
- Former smokers (%): _________________
- Indicate, if known, number of pack/years (p/y) for smokers: _________________

6c) Percentage of HIV patients on the total number of patients (%): _________________

6d) Concomitant diseases (% of the total number of patients)

- COPD (%): _________________
- Asthma (%): _________________
- Bronchiectasis (%): _________________
- Lung cancer (%): _________________
- Past history of tuberculosis (%): _________________
- Heart diseases (%): _________________
- Other lung infections (%): _________________
- Other concomitant diseases (%): _________________

7) Chest CT radiological pattern (indicate the type and site of lesions)

| Lesion Type          | Yes/No | %    | Site 1* | Site 2* | Site 3* |
|----------------------|--------|------|---------|---------|---------|
| Solid nodules        |        |      |         |         |         |
| Cavitated nodules    |        |      |         |         |         |
| Tree-in-bud          |        |      |         |         |         |
| Bronchiectasis       |        |      |         |         |         |
8) Which diagnostic-therapeutic criteria do you follow?
   - American Thoracic Society (ATS) guidelines 2007
   - Domestic protocols
   - Other guidelines (specify): _________________

9) Relationship between clinical presentation and isolation (risk of NTM Pulmonary Disease in patients with NTM isolation)

|                                | Number | %   |
|--------------------------------|--------|-----|
| a) Clinically significant      |        |     |
| (isolation + disease)          |        |     |
| b) Non-clinically significant  |        |     |
| (colonization or contaminants) |        |     |
| c) Indeterminate               |        |     |
| (including unknown and/or      |        |     |
| uncertain)                     |        |     |

10a) What percentage of clinically significant patients (patients at point 9a) is initiated to treatment?
     _________________

10b) Specify, if known, the percentage of clinically significant subjects (isolation + disease) according to the type of NTM isolated:

   - Mycobacterium avium complex (%): _________________
   - Kansasii (%): _________________
   - Xenopi (%): _________________
   - Abscessus (%): _________________
   - Chelone (%): _________________
   - Other (%): _________________
10c) How long is the time between NTM Pulmonary Disease diagnosis and treatment initiation?
   Maximum number of days: _________________
   Minimum number of days: _________________

11) Does your microbiology laboratory perform sensitivity tests to antibiotics?
   Yes
   No

12) Referring to the type of NTM, what antibiotic did you choose?

| Drug 1* | Drug 2* | Drug 3* | Drug 4* |
|---------|---------|---------|---------|
| Mycobacterium avium complex | | | |
| Mycobacterium Kansasii | | | |
| Mycobacterium Xenopi | | | |
| Other NTM (specify): _________________ | | | |

*Answer options: list of antibiotics

13) Adjuvant surgical therapy has been performed?
   Yes
   No
   If yes, specify, if known, the number of cases: _________________

14a) Do you have patients on therapy for at least 6 months?
   Yes
   No
   If yes, specify, if known, the number of cases: _________________

14b) Patients’ outcome after treatment:
Sputum conversion without recurrence or new infection (%): _________________
NTM Persistence (%): _________________
Sputum conversion followed by true relapse (confirmation on genotypic analysis) (%): _________________
Sputum conversion followed by presumed relapse (%): _________________
Sputum conversion followed by new infection (different type of NTM or same type but with different genotype) (%): _________________

15) Other concomitant/adjuvant therapies (in addition to antibiotics):

| Therapy                        | Yes/No | %    |
|--------------------------------|--------|------|
| Respiratory physiotherapy      |        |      |
| Bronchodilator therapy         |        |      |
| Other inhaled therapies        |        |      |
| Mucolytic agents               |        |      |
| Other (Specify)                |        |      |

16) Patient follow-up:
   - Outpatient clinic
   - Day Service
   - Day Hospital
   - Other (please specify): _________________

17) Indicate problems or issues occurred during the diagnostic process and/or treatment:
   - Microbiological tests
   - Patients compliance
   - Adverse events related to treatment
   - Others (specify): _________________

Notes and observations: _________________
REGIONE AREA CITTA' PR STRUTTURA DIVISIONE

LAZIO Centro

119 VENEZIA

120 LAZIO Centro

116 LAZIO Centro

ROMAGNA Centro

40 CAMPANIA

94 EMILIA ROMAGNA

18 CALABRIA Centro

12 BASILICATA

NORD PORDENONE PN A.O.P.N.

SUD BENEVENTO BN ASL

SUD LAMEZIA

SUD PESCOPAGANO PZ P.O.

MT P.O.

BARTOLOMEO RA OSPEDALE

RA OSPEDALE

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DI S. INTENSIVA – MALATTIE INFETTIVE – MALATTIE INTENSIVA

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| TOSCANA | CENTRO |
| TOSCANA | CENTRO |
| SICILIA | CENTRO |
| TOSCANA | CENTRO |
| TOSCANA | CENTRO |
| VENETO | CENTRO |
| VENETO | CENTRO |
| VENETO | CENTRO |
| VENETO | CENTRO |
| VENETO | CENTRO |
| VENETO | CENTRO |
| TRENTINO | |