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**Predictors of starting antimicrobial treatment in patients with nontuberculous mycobacterial lung disease in the Italian scenario: a SITA GIOVANI-IRENE promoted web-survey**

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**Abstract**

The disease burden due to nontuberculous mycobacteria is growing worldwide, consequently to improved diagnostic abilities and an increase in the individuals at risk. Uncertainties exist about the right moment on which start treatment. We investigated the clinical features associated with starting an antimicrobial treatment in patients with nontuberculous mycobacterial lung disease among Italian physicians involved in the field. We found that in real life predictors of starting antimicrobial treatment are quite adherent to international guidelines, with some uncertainties regarding the implication of immunosuppressive drugs.

To the Editor,

Nontuberculous mycobacteria (NTM) are ubiquitous bacteria that can be responsible for severe infections in humans. In developed countries, infections due to NTM are currently more prevalent than those due to *Mycobacterium tuberculosis*.<sup>[1]</sup> The organ most commonly affected are the lungs, with the development of NTM lung disease (NTM-LD).<sup>[2]</sup>

The diagnosis of NTM-LD is hampered by the difficulty in differentiating simple colonisation from disease. On the basis of the ATS/ERS/ESCMID/IDSA guideline, diagnostic criteria require that a patient have characteristic symptoms, compatible radiology, and repeated isolation of NTM. Moreover, other potential causes of pulmonary disease must be excluded.<sup>[3]</sup> However, in clinical practice, fulfilling diagnostic criteria is almost always required before considering treatment, but fulfilling criteria per se is not an adequate rationale for initiating treatment and additional factors are considered. Therefore, relevant differences are encountered in the management of patients with NTM-LD and many choices are based on physicians' personal experience.

We designed a web-survey including demographic, clinical, radiologic, and microbiologic variables, aiming to identify those more frequently recognized as relevant and the weight given to each one of them in the decision of initiate the antimycobacterial therapy. For each variable, we required to provide its significance assigned in a scale from 1 to 5 (1: not relevant, 5: extremely relevant). We administered this survey through the platform [surveymonkey.com](https://www.surveymonkey.com) to members of two Italian networks, SITA (Società Italiana Terapia Antinfettiva) and IRENE (The Italian Registry of Pulmonary Non-tuberculous Mycobacteria), which collect pulmonary and infectious diseases specialists with experience

in the management of both antibiotic treatment and NTM-LD disease. The members of SITA and IRENE are about 400 in total.

Overall, 58 physicians (14.5% of those contacted) involved in the management of NTM-LD answered to our survey, the mean age was 41 years ( $SD\pm 11$ ) and male were the majority ( $n=31$ , 53%). Specialists in infectious diseases were the majority (41, 71%), followed by pulmonologist ( $n=14$ , 24%). Almost half (26, 46%) of the doctors were specialist from less than 5 years, 6 (11%) from 5 to 10 years and 23 (40%) from more than 10 years. Almost all physicians were working in public hospitals ( $n=54$ , 93%), of whom more than half ( $n=27$ , 47%) in a university hospital. Regarding the know-how in NTM-LD, half of the doctors (29, 50%) were prescribing treatment for this disease from less than 5 years, 14 (24%) from 5 to 10 years and 15 (26%) from more than 10 years. The majority of the physicians (29, 50%) evaluated in average less than 5 patients with NTM-LD per year, 18 (31%) 5 to 15 patients per year, 8 (14%) 16 to 30 patients per year and only 3 (5%) more than 30 patients per year.

In figure 1 are reported the variables investigated in our survey and the weight assigned to each one of them.

Regarding demographic, clinical and imaging characteristics, appears interesting the low weight assigned to gender with 33 (57%) and 29 (50%) physicians considering male and female gender as not relevant (rating 1) in their choice, respectively. Instead, classic symptoms of NTM-LD such as dyspnoea, chronic low-grade fever and chronic productive cough were recognized as significant (rating 4-5) by more than 70% of clinicians. Also, the presence of classic NTM-LD signs (cavities at chest X-ray or nodules/bronchiectasis at lung computed tomography) and/or the deterioration of the radiologic picture were considered relevant (rating 4-5) by more than 70% of the physicians.

About microbiological results, the exclusion of alternative diagnosis by microbiologic testing was not considered significant in the choice of starting a specific treatment, with the majority of clinicians assigning a rating of 1 or 2. Instead, the isolation of NTM species in multiple sputum or BAL samples, especially in consecutive samples, was homogeneously considered relevant (rating 4-5) by more than 80% of physicians.

In terms of NTM species, *M. avium* complex, *M. abscessus* subspecies *abscessus* and *M. kansasii* were considered important (rating 4-5) elements in the choice of starting treatment by 75% of those who answered. Isolation of other NTM species received less relevance, with more than half of the physicians assigning a rating of 3 or 4 with *M. gordonae* which was the species which received the lowest significance.

Finally, among comorbidities and treatments, infection by HIV, presence of bronchiectasis and concomitant cystic fibrosis were considered relevant (grading 4-5) by more than 80% of the clinicians. A lower but still significant importance was assigned to concomitant chronic obstructive pulmonary disease and cancer whereas diabetes mellitus and previous tuberculosis received a moderate relevance (rating 2-3) by 50% of the physicians. A homogenous significance was assigned to concomitant immunosuppressive and chemotherapeutic agents use.

Overall, our survey confirms how, due to the rarity of the disease, even among physicians with peculiar interest in NTM-LD, only few are frequently involved in the management of patients with this disease whereas the majority sees only occasional patients. One possible explanation, and this can be a selection bias related to the voluntary participation to this web-survey, is that the prescribers are young and with a limited experience in NTM-LD.

Nevertheless, despite this lack of experience, the predictors of treatment which received the highest rating in our survey are also those elements which international guidelines consider

key factors for the diagnosis of the disease (typical radiologic findings, multiple isolations of NTM, compatible clinical picture).[3,4] Interesting is the relevance assigned to concomitant treatment with immunosuppressive drugs or chemotherapeutics agents is puzzling. As the number and use of these compounds is expanding, a systematic description of the associations reported between these drugs, and NTM-LD will be surely welcomed by clinicians.

However, considering the growing incidence of this disease and the further increase of susceptible individuals expected in the near future, continuous educational activities should be implemented to increase the recognition of NTM-LD, especially by clinicians not used to it, and to improve its management, which should be preferably be directly or indirectly supervised by experts.

It will be interesting to administer the same survey to a broader sample of physicians expert in the management of NTM-LD outside the Italian scenario, to assess, if any, the variations in terms of therapeutic decisions related to different epidemiologic and cultural characteristics.

#### **Declaration of interests**

None related to the content of this article.

#### **Contributions**

A.L., M.C., M.F., L.C., S.A., F.B., A.B., R.B. and A.G. conceived the study. A.L. and M.C. draft the first version of the manuscript. All the authors revised the final version of the manuscript.

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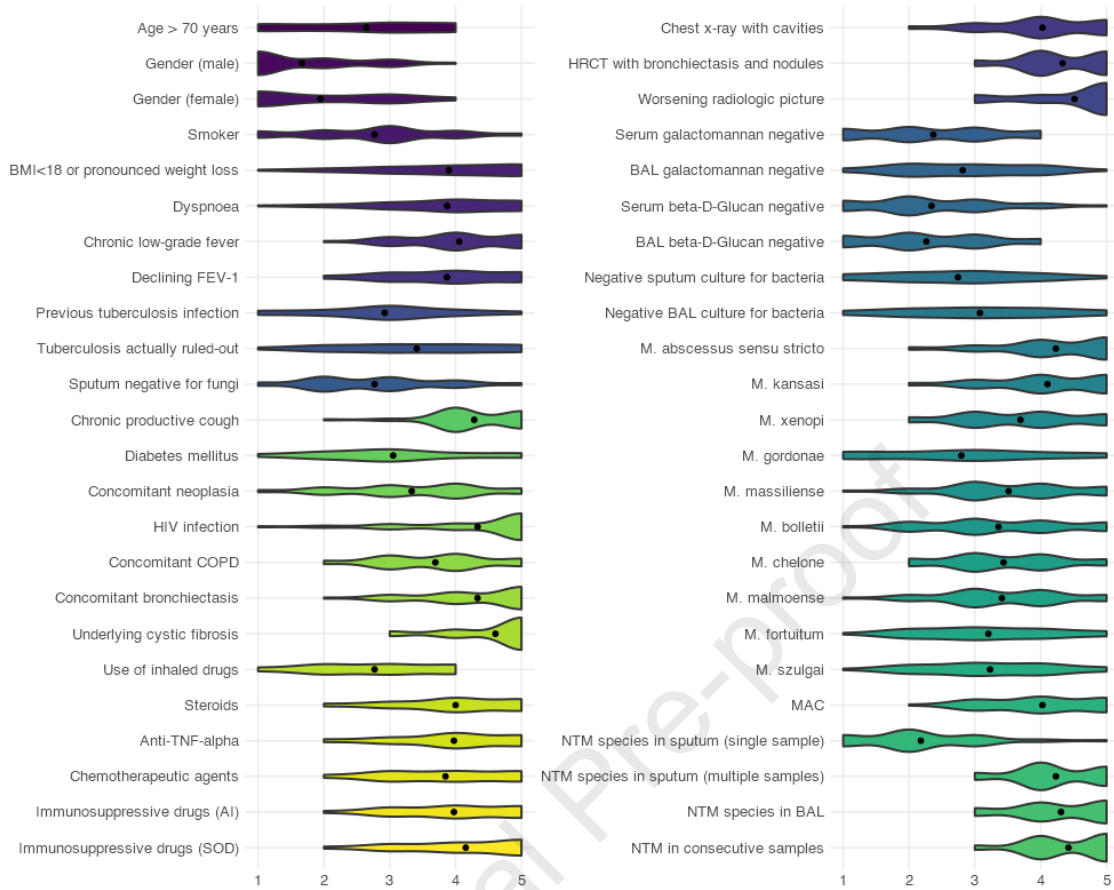
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## Figures

**Figure 1** Percentage of agreement on the weight (from 1 to 5) assigned to treatment predictors subdivided among demographic, clinical and imaging characteristics, microbiological results, NTM species and comorbidities and treatments.

BMI: body mass index; FEV-1: forced expiratory volume in the first second; HRCT: high-resolution computed tomography; NTM: non-tuberculous mycobacteria; BAL: bronchoalveolar lavage; HIV: human immunodeficiency virus; COPD: chronic obstructive pulmonary disease; TNF: tumour necrosis factor; AI: autoimmune disease; SOT: solid organ transplant.

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- Predictors of treatment start for NTM-LD in real life are quite adherent to guideline.
- Due to rarity physicians rarely encounter this disease in daily practice.
- Uncertainties exist about the impact of immunosuppressive drugs.

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