



Beyond pulmonary nontuberculous mycobacteria disease: do extra-pulmonary forms represent an emerging clinical and public health threat?

To the Editor:

Nontuberculous mycobacteria (NTM) are a heterogeneous group of pathogens including all mycobacteria other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae* [1]. The rate of NTM infection has increased substantially over the last decades, especially in high-income countries, as recently illustrated by Diel *et al.* [2] who have highlighted the relevant clinical and economic burden of NTM disease in Germany. The main reasons include the aging of the population, the increasing number of patients with immunodepressive disorders, the use of immunosuppressive agents and a substantial increase in awareness of the disease [3]. Epidemiological data on NTM worldwide are lacking and very few reports have been published based on the Italian population [4, 5].

An assessment of the temporal trends of positive cultures for NTM on one of the two major islands of Italy, Sardinia, has been performed recently in the microbiology laboratory of the University of Sassari, through the collection of data on both *M. tuberculosis* and NTM from January 01 2012 to December 31 2015. Among the 212 positive samples identified during the study period, 162 (76.4%) were positive for *M. tuberculosis* and 50 (23.6%) for NTM. Positive samples were obtained from 126 males (NTM: 27, 21.4%; *M. tuberculosis*: 99, 78.6%) and 83 females (NTM: 23, 27.7%; *M. tuberculosis*: 60, 72.3%) with three subjects being of unknown gender. Patients' median age was 49 years (IQR: 35–71) for the entire cohort, 61 years (IQR: 38–78) for the NTM group and 46 years (IQR: 35–66) for the *M. tuberculosis* group. The lung was the most frequently affected organ for both *M. tuberculosis* (124, 76.5%) and NTM (32, 64.0%). Furthermore, *M. tuberculosis* was also isolated from stomach (15, 9.3%), lymph node (6, 3.7%), skin (5, 3.1%) and urogenital tract (5, 3.1%) samples while NTM were also found in skin (8, 16.0%) and lymph node (7, 14.0%) samples (table 1). The most commonly isolated NTM species was *Mycobacterium avium* (16, 32.0%), followed by *Mycobacterium xenopi* (9, 18.0%), *Mycobacterium gordonae* (8, 16.0%) and *Mycobacterium chelonae* (6, 12.0%). The NTM species isolated from the lung included *M. avium* (10, 31.3%), *M. xenopi* (8, 25.0%) and *M. gordonae* (7, 21.9%), while the NTM isolated from cutaneous samples were *M. chelonae* (5, 62.5%) and *Mycobacterium marinum* (3, 37.5%). Of these last two NTM species, the former was isolated from cutaneous samples in 83.3% of cases, while the latter was isolated only from skin.

Patients with NTM infection were statistically older than patients with *M. tuberculosis* infection (p-value: 0.04) and this finding underlines the importance of age-related immunosurveillance in keeping NTM infections under control. The elderly are more susceptible to developing NTM infection due to immunosenescence, a higher prevalence of immunodepressive diseases and a wider use of immunosuppressive drugs. The skin and the lymph nodes were more often associated with NTM infection (8, 16.0% and 7, 14.0%; p-value: 0.003) compared to infection by *M. tuberculosis* (5, 3.1% and 6, 3.7%; p-value: 0.02), highlighting how NTM are gaining importance in non-pulmonary infections. Among the



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TABLE 1 Prevalence of nontuberculous mycobacteria (NTM) in an Italian cohort, 2012–2015

	Lung	Stomach	Skin	Bone marrow	Lymph nodes	Total
<i>M. avium</i>	10 (62.5, 38.8–86.2)	–	–	1 (6.3, –5.6–82.7)	5 (31.3, 8.6–54.0)	16/50 (32.0, 19.1–44.9)
<i>M. gordonae</i>	7 (87.5, 71.3–100.0)	1 (12.5, –10.4–35.4)	–	–	–	8/50 (16.0, 5.8–26.2)
<i>M. chelonae</i>	1 (16.7, –13.1–46.5)	–	5 (83.3, 53.5–100.0)	–	–	6/50 (12.0, 3.0–21.0)
<i>M. xenopi</i>	8 (88.9, 68.4–100.0)	1 (11.1, –9.4–31.6)	–	–	–	9/50 (18.0, 7.4–28.7)
<i>M. abscessus</i>	2 (100.0, 100.0–100.0)	–	–	–	–	2/50 (4.0, –1.4–9.4)
<i>M. intracellulare</i>	1 (100.0, 100.0–100.0)	–	–	–	–	1/50 (2.0, –1.9–5.9)
<i>M. scrofulaceum</i>	–	–	–	–	2 (100.0, 100.0–100.0)	2/50 (4.0, –1.4–9.4)
<i>M. fortuitum</i>	1 (100.0, 100.0–100.0)	–	–	–	–	1/50 (2.0, –1.9–5.9)
<i>M. marinum</i>	–	–	3 (100.0, 100.0–100.0)	–	–	3/50 (6.0, –0.6–12.6)
<i>M. szulgai</i>	1 (100.0, 100.0–100.0)	–	–	–	–	1/50 (2.0, –1.9–5.9)
<i>M. simiae</i>	1 (100.0, 100.0–100.0)	–	–	–	–	1/50 (2.0, –1.9–5.9)
Total	32 (64.0, 50.7–77.3)	2 (4.0, –1.4–9.4)	8 (16.0, 5.8–26.2)	1 (2.0, –1.9–5.9)	7 (14.0, 4.4–23.6)	–

Data are presented as n (%; 95% CI) unless otherwise stated.

NTM species isolated from cutaneous samples, *M. chelonae* was more prevalent and overcame *M. marinum*, affirming its role as an emerging pathogen in cutaneous infections. NTM infection involved the skin in 16% of cases, as has been reported previously [3, 6, 7]; however, this prevalence is higher than in previous national [5] and local [8] data, demonstrating an increasing diagnostic sensitivity and interest in this topic.

Different points may be drawn from these findings as highlights, namely: 1) *M. chelonae* is emerging as a cutaneous pathogen; 2) Mycobacterial cutaneous infections are nowadays more commonly due to NTM than *M. tuberculosis*; 3) A multidisciplinary approach, higher diagnostic accuracy in the laboratory setting and increasing awareness in the notification of the public health authorities are needed. Finally, NTM-derived lung disease remains an important field for future clinical research and patients' initiatives and international registries, such as the Bronchiectasis and NTM Research Registry in the United States or the Italian REgistry of pulmonary Non-tuberculous mycobactEria (IRENE) [9, 10], might play a crucial role in improving our knowledge of the epidemiologic situation, which will in turn help create control programmes for these patients.

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