

## Original Article

## Non-Tuberculous Mycobacteria. An Emerging Threat? ☆



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## ARTICLE INFO

## Article history:

Received 28 October 2016

Accepted 27 February 2017

Available online 31 August 2017

## Keywords:

Non-tuberculous mycobacteria  
Non-tuberculous mycobacteria infection  
Mycobacteriosis  
*Mycobacterium kansasii*  
*Mycobacterium avium* complex

## ABSTRACT

**Introduction and objective:** Non-tuberculous mycobacteria (NTM) isolates are becoming more common. The main objective of our study was to establish the number and diversity of NTM species in our region and their distribution according to the source sample, age and gender of the patients, and to analyze clinically significant isolates.

**Methodology:** Prospective study of all NTM isolated in Asturias from 2005 to 2012. Samples were processed following internationally accepted guidelines. Statistical analysis was based on Fisher's exact test for 2×2 contingency tables.

**Results:** A total of 3284 mycobacteria were isolated: 1499 *Mycobacterium tuberculosis* complex (MTB) and 1785 NTM. During the study, NTM isolation rates increased while MTB isolation decreased. NTM were more frequent in men ( $p<0.001$ ). *M. gordonae* was the most frequently isolated species but did not cause disease in any case. NTM isolates from 212 patients were associated with clinically significant disease (17.1%). *M. kansasii* and *M. avium* were most commonly associated with disease. The number of *M. kansasii* isolates from men was statistically significant ( $p<0.01$ ).

**Conclusions:** In our study, NTM isolates increased by 35%, compared with a 21% decline in cases of MTB. Both isolation of NTM and clinically significant cases were more common in men. Only 17.1% of NTM isolates were associated with disease, most commonly *M. avium* complex and *M. kansasii*.

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## Micobacterias no tuberculosas. ¿Una amenaza emergente?

## RESUMEN

**Introducción y objetivo:** Los aislamientos de micobacterias no tuberculosas (MNT) son cada vez más frecuentes. El objetivo principal de nuestro estudio fue conocer el número y la variedad de especies de MNT en nuestra región, su distribución según el origen de la muestra, y la edad y sexo de los pacientes; asimismo, analizar pormenorizadamente los aislamientos clínicamente significativos.

**Metodología:** Estudio prospectivo que incluye todas las MNT aisladas en Asturias durante el período 2005–2012. Las muestras se procesaron siguiendo directrices internacionalmente aceptadas. Para el tratamiento estadístico de los datos se utilizaron tablas de contingencia 2×2 aplicando el test exacto de Fisher.

## Palabras clave:

Micobacterias no tuberculosas  
Infecciones por *Mycobacterium*  
Mycobacteriosis  
*Mycobacterium kansasii*  
*Mycobacterium avium* complex

☆ Please cite this article as: Martínez González S, Cano Cortés A, Sota Yoldi LA, García García JM, Alba Álvarez LM, Palacios Gutiérrez JJ, et al. Micobacterias no tuberculosas. ¿Una amenaza emergente? Arch Broncopneumol. 2017;53:554–560.

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**Resultados:** Se aislaron 3.284 micobacterias: 1.499 *Mycobacterium tuberculosis* complex (MTB) y 1.785 MNT. A lo largo del estudio se incrementaron los aislamientos de MNT y se redujeron los de MTB. Los aislamientos de MNT fueron más numerosos en hombres que en mujeres ( $P < 0,001$ ). *M. gordonae*, la especie más frecuentemente aislada, no originó enfermedad en ningún caso. El aislamiento fue clínicamente significativo en 212 pacientes (17,1%), siendo *M. kansasii* y *M. avium* las especies que más frecuentemente causaron enfermedad. La diferencia de aislamientos de *M. kansasii* entre mujeres y hombres fue estadísticamente significativa ( $p < 0,01$ ).

**Conclusiones:** En nuestro estudio, los aislamientos de MNT se incrementaron un 35%, frente a un descenso del 21% de los casos de MTB. Tanto los aislamientos de MNT como los casos clínicamente significativos fueron más frecuentes en hombres. Solo un 17,1% de las MNT aisladas, principalmente *M. avium* complex (MAC) y *M. kansasii*, ocasionaron enfermedad.

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## Introduction

Non-tuberculous mycobacteria (NTM) have gained prominence in recent years, and now account for between 30% and 50% of the total number of mycobacteria isolated in microbiology laboratories<sup>1</sup>; this phenomenon may be associated with an increased incidence of disease caused by NTM. The reasons for this increase are not entirely clear. The introduction of automated liquid culture systems in mycobacteria laboratories in the 1990s may have played a decisive role in improving diagnostic yield,<sup>2–4</sup> although in their first decade of continued use no such dramatic increase in NTM isolation rates was reported.<sup>5–15</sup> In general, data on the incidence and prevalence of NTM are scant<sup>2</sup> and probably determined by the ability of each laboratory to isolate these organisms and the available diagnostic tools.

More than 170 species of mycobacteria have been described to date (<http://www.bacterio.cict.fr/m/mycobacterium.html>).

The most frequently isolated species are *Mycobacterium avium* complex (MAC), *M. gordonae*, *M. kansasii*, *M. marinum*, *M. xenopi*, *M. fortuitum*, *M. chelonae* and *M. abscessus*.

Generally, most isolates are not clinically significant, but a recent study in the United States showed that the number of deaths from disease due to NTM was increasing.<sup>5</sup> It is important to assess the significance of the isolates by analyzing their specific clinical context in line with the recommendations of internationally recognized scientific societies, such as the American Thoracic Society (ATS), the British Thoracic Society (BTS) and the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).<sup>16–18</sup>

Some diseases are often listed among the risk factors for mycobacterial infection: chronic obstructive pulmonary disease (COPD), pneumoconiosis, bronchiectasis, previous tuberculosis, post-radiotherapy fibrosis, chronic pulmonary aspiration (esophageal disease), cystic fibrosis, immune deficiency, HIV infection, alcoholism, cancer (lung or other sites), and diabetes mellitus. However, it should be noted that a high percentage of patients present no risk factors.<sup>2,5,16</sup>

The aim of this study was to determine the number and diversity of NTM species isolated in our region and their distribution according to the source of the sample, and the age and gender of the patient. Clinically significant isolates were also analyzed in detail.

## Methodology

This was a prospective study that included all mycobacteria isolated in Asturias (Spain) during the period 2005–2012. Isolates came from the 8 public hospitals in the region (mean population of 1,079,626 inhabitants) that systematically submit the isolated strains to the Regional Mycobacteria Reference Unit for identification and/or sensitivity testing.

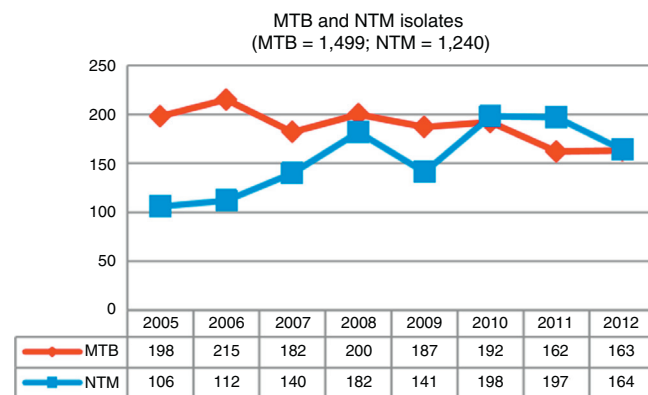


Fig. 1. MTB and NTM isolates, 2005–2012.

Protocols following internationally accepted guidelines (American Society for Microbiology [ASM])<sup>19</sup> were used for the initial processing of the clinical samples.

The commercially available preparation BBL MycoPrep<sup>®</sup> (Specimen Digestion/Decontamination Kit, Becton-Dickinson) was used for the pretreatment digestion-decontamination phase.

Solid culture media (Löwenstein-Jensen) and liquid media with automated reading systems (BACTEC<sup>™</sup> MGIT<sup>™</sup> 960 [*Mycobacterial Growth Indicator Tube*] and/or Bact/ALERT<sup>®</sup> MP), were used for culture, according to the methodology of each hospital.

Species level identification was carried out using off-the-shelf techniques combining PCR and reverse hybridization (INNO-LiPA<sup>®</sup> Mycobacteria V2 and GENOTYPE<sup>®</sup> Mycobacterium CM/AS) and proprietary techniques (PRA<sup>20</sup> 16S-23S rRNA<sup>21</sup>) combining PCR-RFLP. Sequencing was not required in any of the clinically significant cases.

The criteria listed in the ATS/IDSA 2007 guidelines<sup>16</sup> were used to define a case as clinically significant. For statistical analysis of the data, 2×2 contingency tables were used to verify the independence of dichotomous variables, applying the Fisher's exact test. A value of  $P < 0.05$  was considered statistically significant.

## Results

During the study period, 3,284 mycobacteria isolated from 37,041 clinical samples were identified: 1,499 (45.7%) were *M. tuberculosis* complex (MTB) and 1,785 (54.3%) were NTM. Fig. 1 shows changes in the number of isolates by mycobacteria groups over the 8-year period of analysis; a growing trend for NTM and a waning trend for MTB can be observed.

In total, 1,785 NTM isolates were obtained from samples from 1,240 patients; 898 were men (72.4%) and 342 were women (27.6%). Mean patient age was 65 years (66.6 for men and 63.6 for women).

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