NTM lung disease: a serious problem we should always be aware of

NTM, nontuberculous mycobacteria.

Online activity details

This resource has been downloaded from a touchEXPERT BRIEFING, hosted on touchRESPIRATORY website. The full activity, which includes video resources, can be accessed at:

https://www.touchrespiratorytmc.com/airway-and-lung-infection/learning-zone/ntm-lung-disease-a-serious-problem-we-should-always-be-aware-of/

This content is for healthcare professionals only.

Learning objectives

After watching the touchEXPERT BRIEFING activity, you should be better able to:

- ✓ Describe the significant burden of NTM lung disease for patients, in terms of increased mortality and morbidity and reduced quality of life
- ✓ Recall how NTM influences declining lung function over time and the importance of a multidisciplinary approach to NTM management to optimise outcomes
- ✓ Recognise the low level of disease awareness for NTM lung disease and how this may be improved

Expert faculty

Prof. Stefano Aliberti

Humanitas Research Hospital

Humanitas University, Milan, Italy

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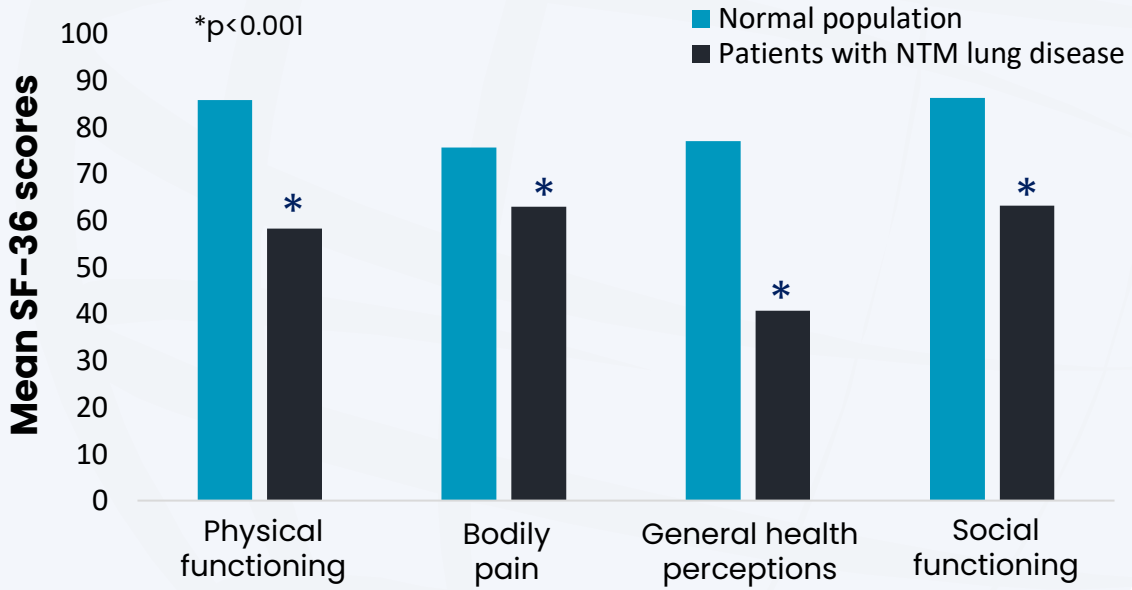
The impact of NTM lung disease

Burden of NTM lung disease

- The annual prevalence of NTM lung disease ranges from 0.2–9.8/100,000, though this is likely underestimated[1]
- NTM lung disease is associated with increased morbidity and mortality[2,3]
  - Results in progressive deterioration in lung function[2,3]
  - Can develop into a fulminant, rapidly progressive condition that can be fatal[3]
- Quality of life is also significantly impaired in patients with NTM lung disease[4]

Health-related quality of life in 51 patients with NTM lung disease from an ambulatory clinic in Canada (SF-36)[4]



SF-36, medical outcomes short-form – 36 version 2.

1. Chindam A. et al. J Clin Tuberc Other Mycobact Dis 2021;25:100271; 2. Lee MR, et al. PLoS One 2013; 8:e58214; 3. Griffith DE, et al. Am J Respir Crit Care Med 2007;175:367–416; 4. Mehta M, Marras TK. Respir Med 2011;105:1718–25.

Impact of NTM lung disease in patients with concomitant lung conditions / undergoing surgery

Bronchiectasis*

- Significant pulmonary function decline (mean: 48 mL/year) with NTM lung disease and concomitant bronchiectasis, especially in young, male patients with a high radiographic score[1]
- Worsening disease severity and decrease in patient quality of life, due to an increase in both respiratory and systemic signs and symptoms[2]
- In rare cases patients may require O_2 therapy or non-invasive mechanical intubation, and even experience chronic respiratory failure[2]

Cystic fibrosis

- Patients with cystic fibrosis experience chronic bacterial infection, so NTM lung disease can be hard to detect[2]
- As such, screening for NTM lung disease is recommended at least once a year year[3]
- In addition, if there is a decrease in lung function or a worsening of cystic fibrosis signs or symptoms, NTM lung disease should be suspected and tested for[2]

Lung transplantation

- Following lung transplantation, NTM infection is a high risk due to immunosuppression, high morbidity risk, and the complex treatment regimens required[1]
- NTM infection can occur at any time following lung transplantation[2]
- NTM infection could lead to acute or chronic transplant rejection[2]
- Treatment should be considered based on individual characteristics, disease status, the pathogens involved, and patients monitored closely for any drug–drug interactions[2]

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*non cystic-fibrosis bronchiectasis.

1. Lee MR, et al. PLoS One 2013; 8:e58214; 2. Expert opinion from Prof Stefano Aliberti – video available at https://www.touchrespiratorytmc.com/airway-and-lung-infection/learning-zone/ntm-lung-disease-a-serious-problem-we-should-always-be-aware-of/ ; 3. Low D, et al. J Cystic Fibrosis 2020;19:569–574.

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Raising awareness of NTM lung disease

Diagnosis of NTM lung disease (1)

- Diagnosis of NTM lung disease can be a challenge, as the symptoms are variable and non-specific[1]
- The most common clinical presentation is pulmonary disease, often in the setting of underlying structural airway diseases such as bronchiectasis or COPD[2]
- As such, a confirmed diagnosis requires a combination of clinical, radiographic and microbiology findings, as well as the exclusion of any other causes[1–3]

COPD, chronic obstructive pulmonary disease.

1. Griffith DE, *et al. Am J Respir Crit Care Med* 2007;175:367–416; 2. Daley CL, *et al. Clin Infect Dis* 2020;71:e1–e36; 3. Haworth CS, *et al. Thorax* 2017;72:ii1–ii64.

Diagnosis of NTM lung disease (2)

Criteria for diagnosis of NTM lung disease[1–3]

Clinical / Radiologic

- Pulmonary or systemic symptoms

+

- Nodular or cavitary opacities on chest radiograph, or a high-resolution CT scan that shows bronchiectasis with multiple small nodules

Diagnostic

- Appropriate exclusion of other diagnoses

Microbiologic

- Positive culture results from at least two separate expectorated sputum samples. If the results are nondiagnostic, consider repeat sputum AFB smears and cultures

or

- Positive culture results from at least one bronchial wash or lavage

or

- Transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy

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AFB, acid-fast bacilli; COPD, chronic obstructive pulmonary disease.

1. Griffith DE, *et al. Am J Respir Crit Care Med* 2007;175:367–416; 2. Daley CL, *et al. Clin Infect Dis* 2020;71:e1–e36; 3. Haworth CS, *et al. Thorax* 2017;72:ii1–ii64.

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Improving awareness of NTM lung disease

- Increasing awareness of NTM lung disease can help identify cases and improve clinical outcomes and quality of life[1]
- Awareness should be increased not just for physicians and pulmonologists, but across the whole multidisciplinary team involved in lung care (e.g., radiologists, physiotherapists, clinical microbiologists, ENT specialists) as well as Patient Awareness groups[1]
- While it is difficult to detect NTM lung disease as it often occurs in patients with concomitant long conditions,[2,3] changes in the patient's condition may indicate NTM infection:
  - An increase of worsening of existing (lung) signs/symptoms[1]
  - New signs or symptoms (lung)[1]
  - New radiological findings or a progression of radiological disease markers[1]
- Regular screening for NTM lung disease is recommended in patients with chronic lung conditions, such as cystic fibrosis[1,4]

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ENT, ear nose and throat.

1. Expert opinion from Prof Stefano Aliberti – video available at https://www.touchrespiratorytmc.com/airway-and-lung-infection/learning-zone/ntm-lung-disease-a-serious-problem-we-should-always-be-aware-of/
; 2. Griffith DE, et al. Am J Respir Crit Care Med 2007;175:367–416; 3. Daley CL, et al. Clin Infect Dis 2020;71:e1–e36; 4. Low D, et al. J Cystic Fibrosis 2020;19:569–574.

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Expert opinion: What advice can you provide for physicians to help increase the detection of NTM lung disease?

"Physicians should be aware of the prevalence of NTM (in both healthy patients and those with existing lung conditions) and its symptoms, e.g., chronic or subacute cough, sputum production, etc., as well as systemic symptoms such as weight loss and asthenia"

"As well as positive clinical and radiological signals, microbiological assessment is fundamental to the detection/diagnosis of NTM lung disease"

Summary quotations based on an expert interview with Prof. Stefano Aliberti – video available at https://www.touchrespiratorytmc.com/airway-and-lung-infection/learning-zone/r lung-disease-a-serious-problem-we-should-always-be-aware-of/

Learnings from the COVID-19 pandemic

Successful implementation of telemedicine for virtual monitoring and assessment

Conventional clinic assessments are still essential, especially for treatment decision discussions, microbiology and long term follow-up

Expert opinion from Prof. Stefano Aliberti – video available at https://www.touchrespiratorytmc.com/airway-and-lung-infection/learning-zone/ntm-lung-disease-a-serious-problem-we-should-always-be-aware-of/

Summary

1. NTM lung disease is a serious condition that has a substantial impact on patient mortality, morbidity, and quality of life[1–3]
2. Diagnosis of NTM lung disease is a challenge;[2] increasing awareness of NTM lung disease could help identify cases and improve clinical outcomes and quality of life[4]
3. Increased awareness and detection can be achieved by education of healthcare workers across the multidisciplinary team on both specific and systemic signs and symptoms[4]
4. The successful implementation of telemedicine during the COVID-19 pandemic has provided a platform for continued virtual monitoring and assessment[4]

1. Lee MR, et al. PLoS One 2013; 8:e58214; 2. Griffith DE, et al. Am J Respir Crit Care Med 2007;175:367–416; 3. Mehta M, Marras TK. Respir Med 2011;105:1718–25; 4. Expert opinion from Prof. Stefano Aliberti – videos available at https://www.touchrespiratorytmc.com/airway-and-lung-infection/learning-zone/ntm-lung-disease-a-serious-problem-we-should-always-be-aware-of/

Online activity details

This following slides summarise the video interviews from the following touchEXPERT BREIFING. The full activity, which includes video resources, can be accessed at:

https://www.touchrespiratorytmc.com/updates-on-nontuberculous-mycobacteria/

This content is for healthcare professionals only.

Learning objectives

After watching the touchEXPERT BRIEFING activity, you should be better able to:

- ✓ Recognise the low level of disease awareness and how this can extend the time to a definitive diagnosis of nontuberculous mycobacteria (NTM) lung disease
- ✓ Describe the significant burden of NTM for patients, in terms of increased mortality and morbidity and reduced quality of life
- ✓ Recall how NTM influences declining lung function over time and the importance of a multidisciplinary approach to NTM management to optimise outcomes

Expert faculty

Prof. James Chalmers

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Dundee, Scotland, UK

Prof. Stefano Aliberti

Humanitas Research Hospital

Humanitas University, Milan, Italy

Dr Arietta Spinou

King's College London

London, England, UK

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NTM lung disease is associated with increased morbidity and mortality

Prof. James Chalmers & Dr Arietta Spinou

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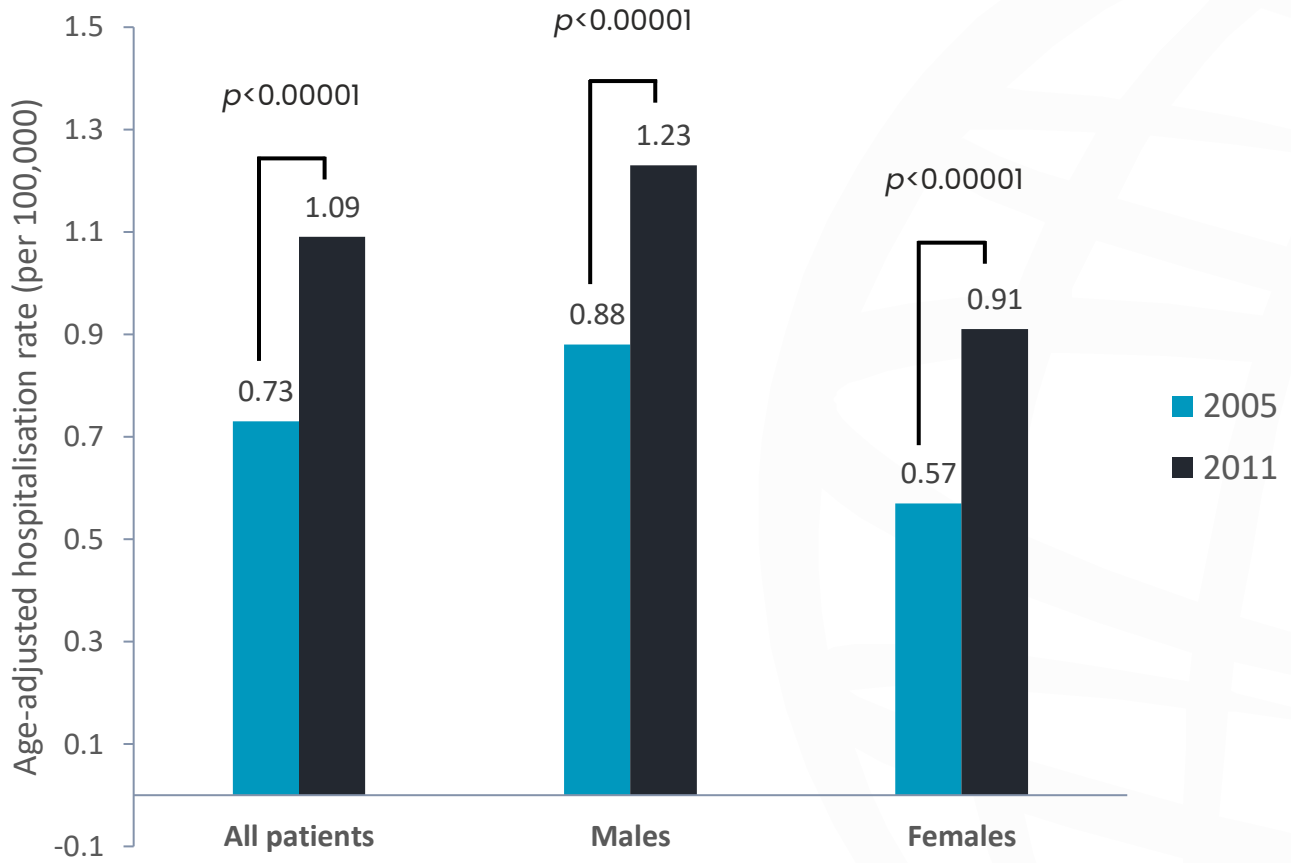
Increasing hospitalization rate in patients with NTM-LD



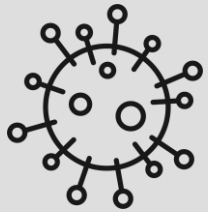
From 2005 to 2011, the annual number of NTM-LD-associated hospitalizations in Germany increased by 4.9% on average, with an age-adjusted increase of 5.9%

NTM-LD, non-tuberculous mycobacterial lung disease.
Adapted from Ringshausen FC, et al. BMC Infect Dis 2013;13:231.

Common symptoms of NTM-LD

Clinical symptoms

Chronic cough[1]

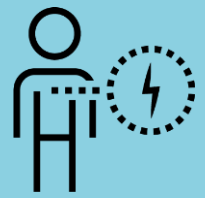


Purulent sputum[1]

Breathlessness[2]

Systemic symptoms

Haemoptysis[1]



Fatigue[1]

Weight loss[1]

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1. Johnson M & Odell J. J Thorac Dis. 2014;6:210–220; 2. Loebinger M et al. ERJ 2018;52:PA348.

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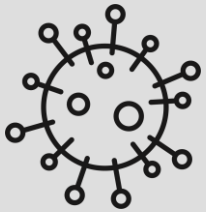
Common symptoms of NTM-LD

Clinical symptoms

Chronic cough[1]

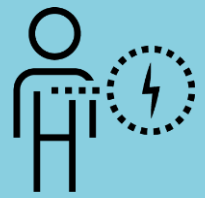


Purulent sputum[1]

Breathlessness[2]

Systemic symptoms

Haemoptysis[1]



Fatigue[1]

Weight loss[1]

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1. Johnson M & Odell J. J Thorac Dis. 2014;6:210–220; 2. Loebinger M et al. ERJ 2018;52:PA348.

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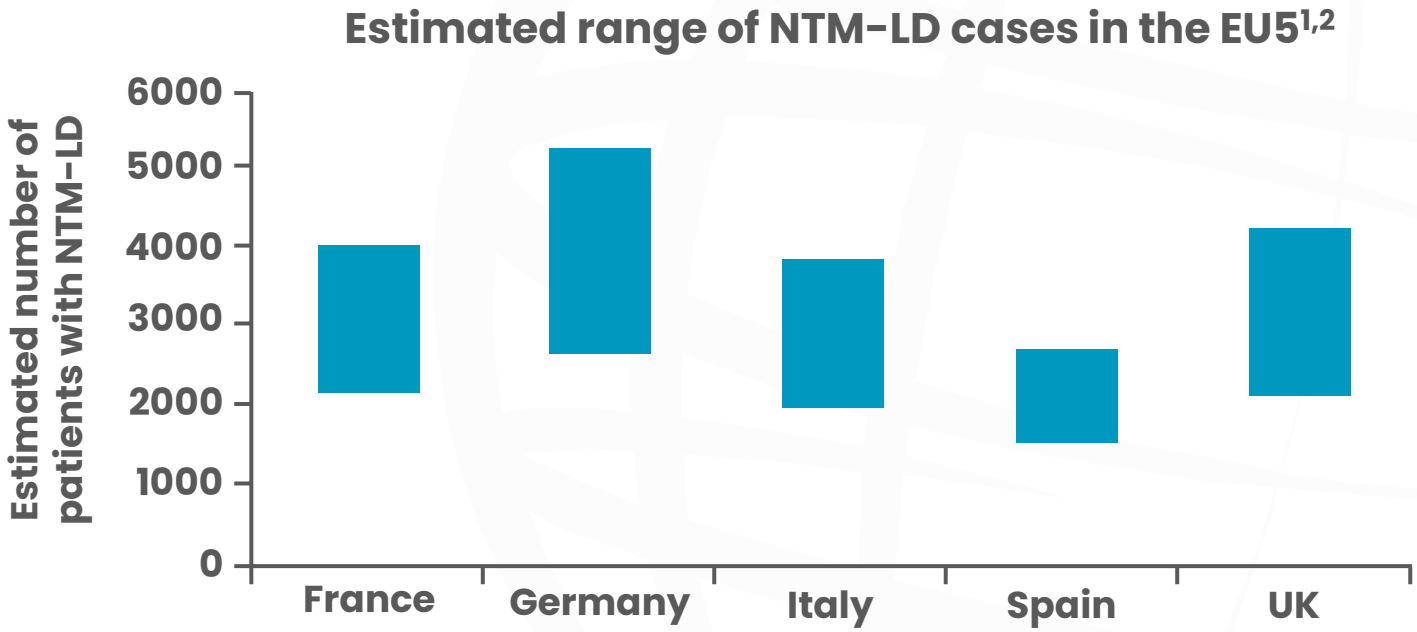
Prevalence of NTM-LD is underestimated

Annual NTM-LD prevalence is reported as 3.3–6.2 per 100,000 in European countries[1,2]

This is below the threshold for orphan disease clasification[3]

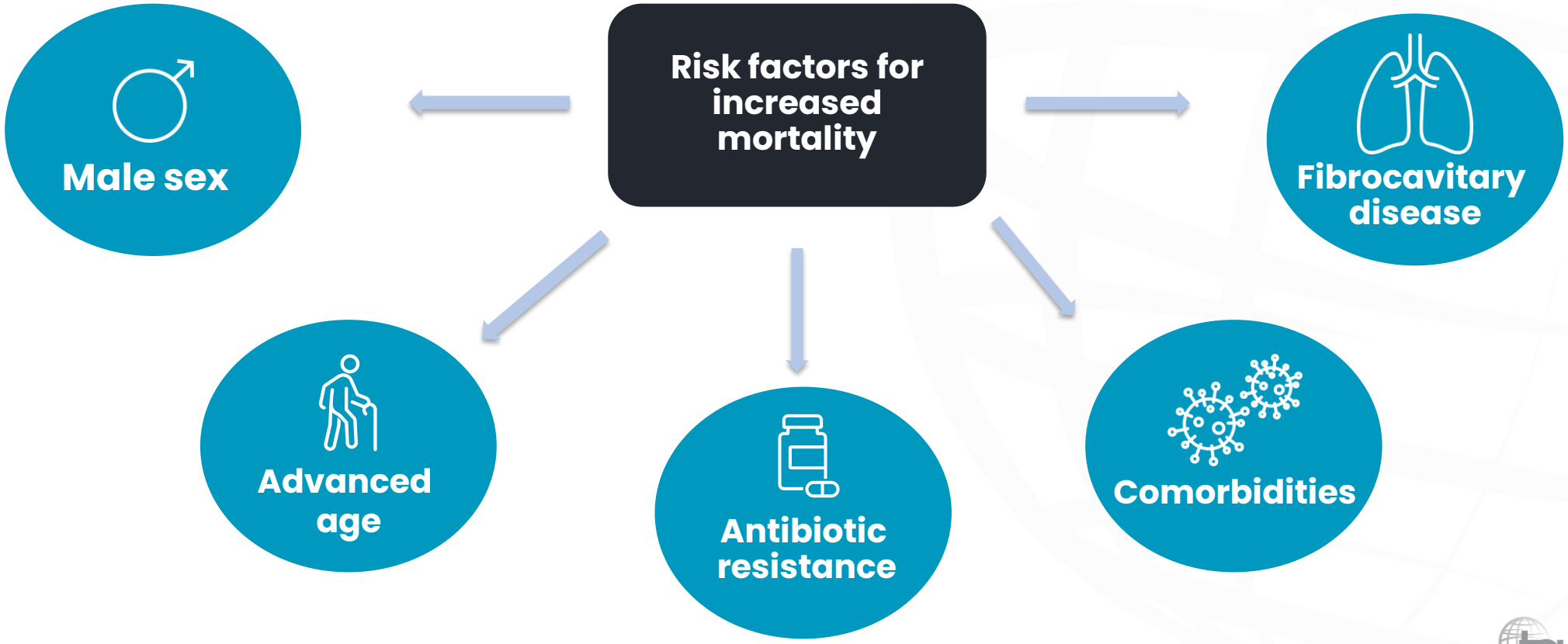
However, the prevalence of NTM-LD is now greater than that of tuberculosis, having increased over the past 30 years[4,5]



1. Wagner D, et al. Poster (P1067) presented at: ERS International Meeting; September 6-10, 2014; Munich, Germany; 2. Ringshausen FC, et al. Emerg Infect Dis 2016; 22:1102-5; 3. Public summary of opinion on orphan designation: Amikacin sulfate for the treatment of nontuberculous mycobacterial lung disease. 2014. (Accessed February, 2018, at http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2014/05/ WC500166122.pdf.); 4. Marras TK, et al. Thorax 2007; 62:661-6; 5. Adjemian J, et al. Am J Respir Crit Care Med 2012; 186:553-8.

Risk factors for mortality in patients with NTM-LD

A pooled analysis revealed a five-year overall mortality of 32% (95% CI 25–39%) in patients with MAC NTM-LD



CI, confidence interval; MAC, Mycobacterium avium complex.
Diel R, et al. BMC Infect Dis. 2018;18:206; v.d. Laan R, Obradovic M, Poster DGP-Kongress 2017, Stuttgart, Deutschland.

The impact of undiagnosed or untreated NTM lung disease

Prof. Stefano Aliberti & Prof. James Chalmers

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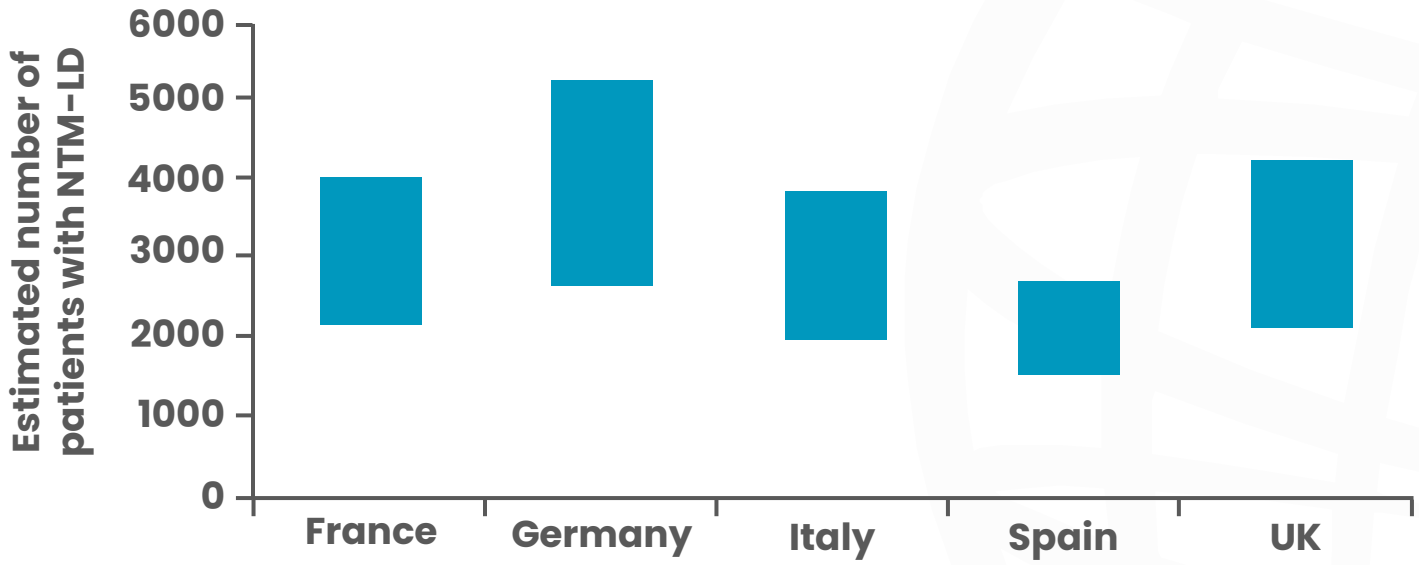
In Europe, the prevalence of NTM-LD is increasing, but still potentially underestimated

Estimated range of NTM-LD cases in the EU5[1,2]

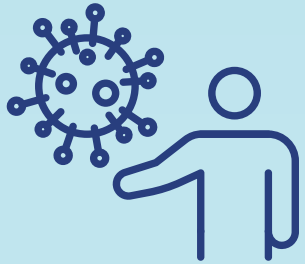


The annual prevalence of NTM-LD is 3.3–6.2 per 100,000 people in EU5 countries[1,2]

1. Wagner D, et al. Poster (P1067) presented at: ERS International Meeting; September 6-10, 2014; Munich, Germany; 2. Ringshausen FC, et al. Emerg Infect Dis 2016; 22:1102-5.

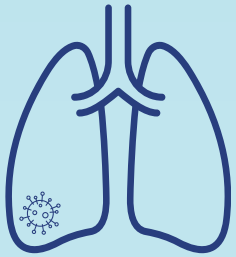
The true prevalence of NTM-LD may be higher than currently estimated

A meta-analysis of eight studies captured 1,492 patients with bronchiectasis (age range 13–88 years)[1]



NTM-LD prevalence was calculated as 9.3%[1]

In real-world practice, as many as 9 out of 10 cases of NTM-LD may not yet have been diagnosed[2]



This suggests that NTM-LD may be relatively common in patients with bronchiectasis[1]

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1. Chu H, et al. Arch Med Sci. 2014;10:661–668; 2. Authors own opinion.

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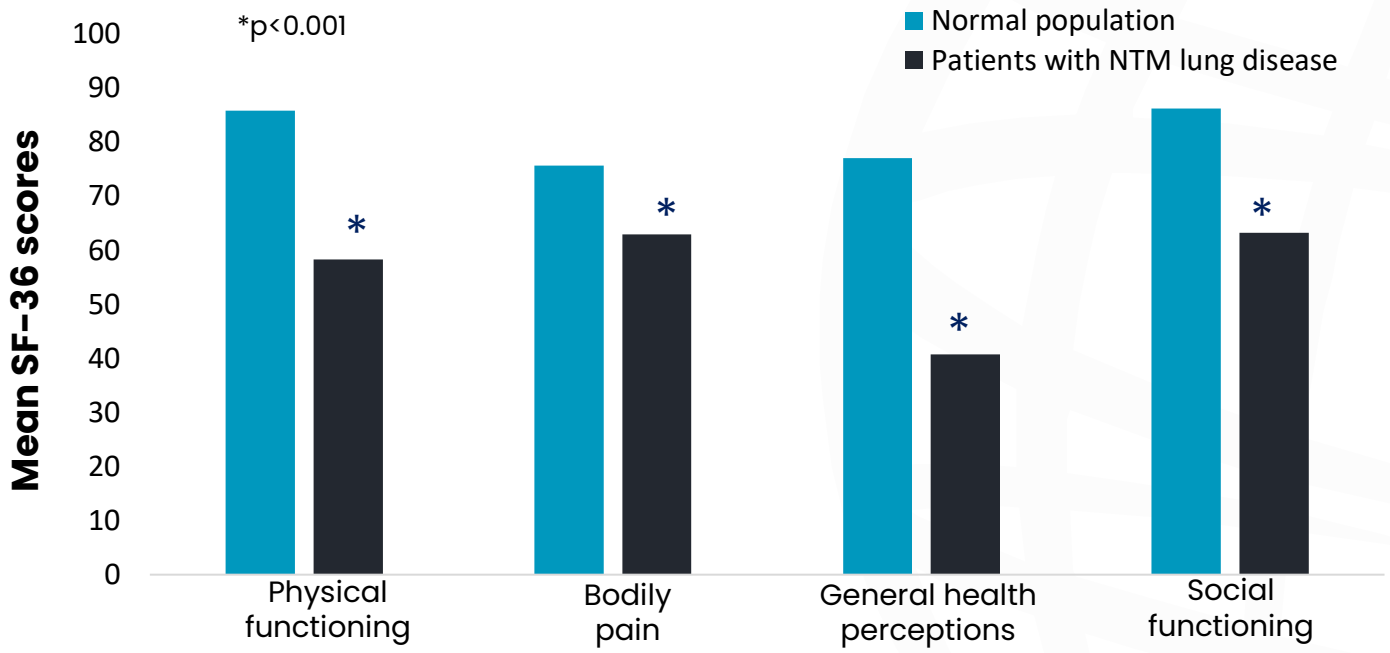
Quality of life is reduced in patients with NTM-LD

Health-related quality of life in 51 patients with NTM lung disease from an ambulatory clinic in Canada (SF-36)[1]



Quality of life is significantly worse in patients with NTM-LD[1]
Cough, fatigue and breathlessness impact most daily activities[2]

†Study period 08/2008-07/2009.
1. Mehta M, Marras TK. Respir Med 2011; 105:1718-25; 2. Author's own opinion.

NTM lung disease contributes to progressive lung function decline

Prof. Stefano Aliberti & Dr Arietta Spinou

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NTM-LD can be a progressive, and ultimately lethal, lung disease

NTM-LD can become a progressive lung disease[1,2]

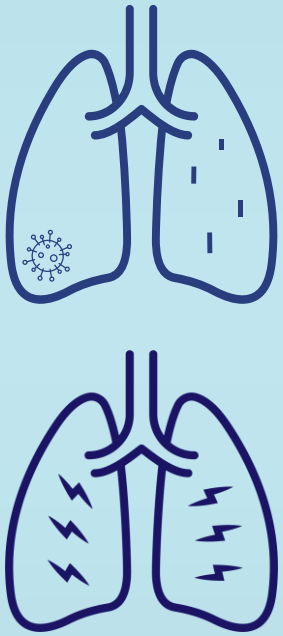
Decline in lung function among patients with NTM-LD (n=68)*[3]

- Mean reduction in FEV_1 was 48 mL/year
- Normal range = 28.4–35.6 mL/year

The decline in lung function in patients with NTM-LD is closely associated with a worsening in quality of life[4]

* Study from Taiwan (01/2000 – 04/2011).
FEV_1, forced expiratory volume in 1 sec.
1. Weiss CH, Glassroth J. Expert Rev Respir Med 2012; 6:597-612; 2. Griffith DE, et al. Am J Respir Crit Care Med 2007; 175:367-416; 3. Lee MR, et al. PLoS One 2013; 8:e58214; 4. Mehta M, Marras TK. Respir Med 2011; 105:1718-25.

Decline in lung function may be predicted by parameters other than FEV_1



Patients with NTM-LD often have multiple impaired aspects of pulmonary function, including:[1]

- Obstruction
- Gas trapping
- Low DLCO

Alongside FEV_1, TLC and RV are also valuable measures of lung function decline

DLCO, low diffusion of carbon monoxide; RV, residual volume; TLC, total lung capacity.
Author's own opinions.
1. Mehta M, et al. Respirology. 2015;20:987–93.

Clear risk factors exist for lung function decline in patients with NTM-LD

Factors associated with the amount of annual FEV_1 decline in patients with NTM pulmonary disease, by linear regression analysis.

Variables	*p* value
Age	*<0.001*
Gender: male vs. female	*0.018*
Radiographic pattern: bronchiectasis vs. cavity	*0.035*
Radiographic score: >3 vs. ≤3	*0.049*
Baseline function: FEV_1 > 50% VS. FEV_1 ≤50%	*0.002*

NOTE. *NTM, non-tuberculous mycobacteria; forced expiratory volume in 1 second.*

NTM-LD is particularly associated with lung function decline in young, male patients with bronchiectasis and in those with a high radiographic score

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Study of 68 patients with at least two pulmonary function tests within a mean follow-up period of 47 months.
Meng-Rui Lee et al. PLoS One. 2013; 8(3): e58214.

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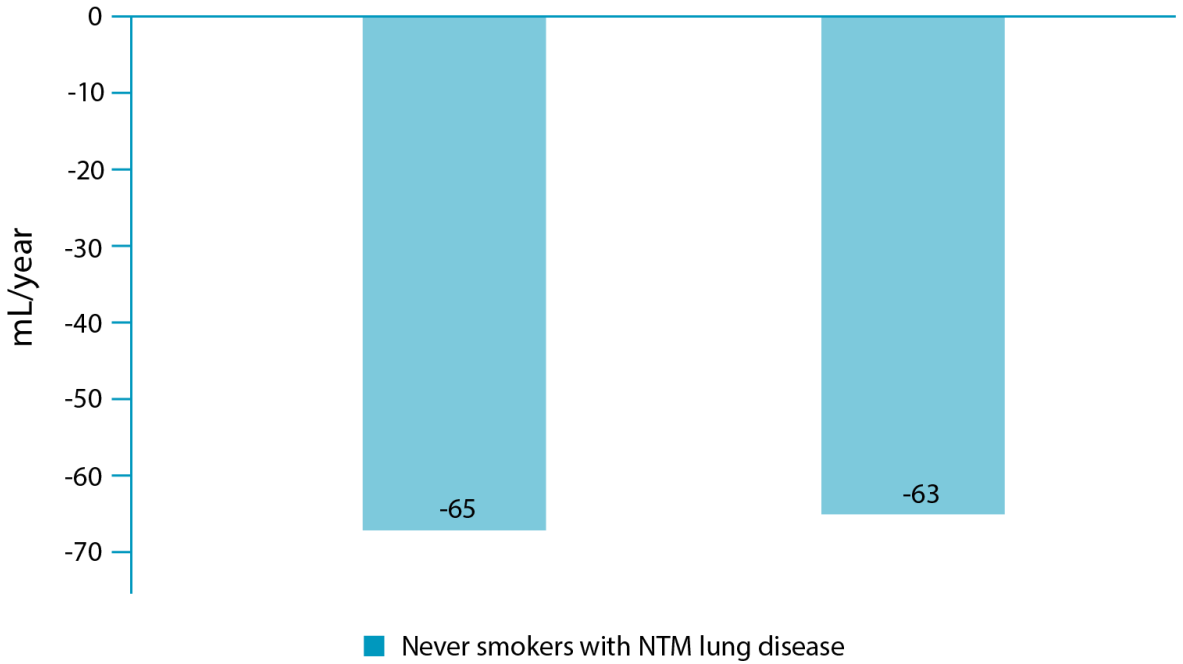
FEV_1 declines in asymptomatic NTM-LD never-smokers

Median change in lung function (FEV_1 and FVC) in patients with NTM-LD who have never smoked

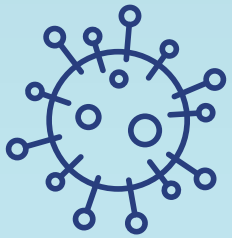


Lung function decline was greater in never-smokers *with* NTM-LD than in never-smokers *without* NTM-LD

(FEV_1: −70 *vs* +20 mL/year; $p = 0.07$)

Retrospective study in 22 NTM-LD patients who have never smoked.
FVC, forced vital capacity.
Kobayashi T et al. J Clin Tuberc Other Mycobact Dis. 2018; 11: 17–21.

Key steps in limiting lung function decline



Improving airway clearance can help minimize the impact of sputum plugs

Intensifying airway clearance techniques is effective in improving respiratory symptoms and lung function[1]

Physiotherapy can also benefit from CT scans to determine areas of sputum collection, to aid effective escalation of treatment plans

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Author's own opinions.

1. Basavaraj A, et al. Int J Respir Pulm Med. 2017;4(1).

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Beyond pharmaceutical intervention: physiotherapy and lifestyle in NTM lung disease

Dr Arietta Spinou & Prof. Stefano Aliberti

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Airway clearance is important to patients

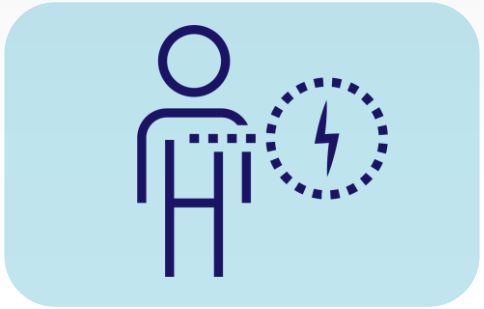
- Research into patient-centric priorities in NTM-LD management emphasizes the role of airway clearance in day-to-day life
- Patients strongly believed that exercise and airway clearance techniques improve their ability to function
- Determining the most effective airway clearance method was identified as a key goal for patients

Henkle E, et al. Ann Am Thorac Soc. 2016;13:S379–84.

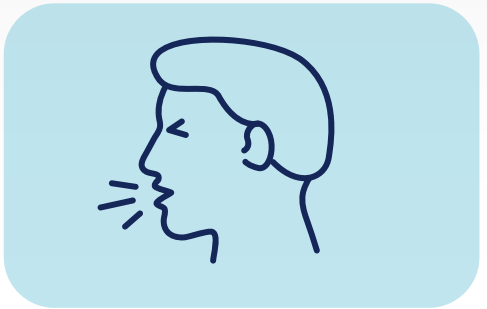
Practical endpoints for assessing the impact of respiratory physiotherapy

Overall quality of life

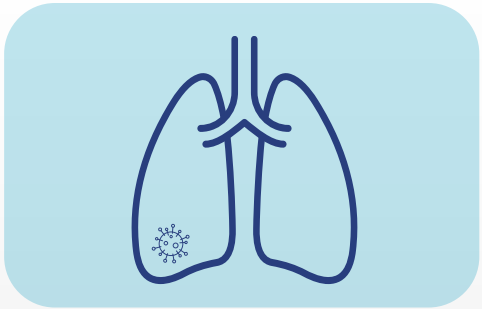
- Day-to-day quality of life
- Symptom control



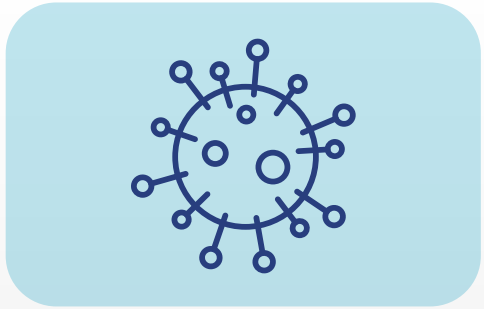
Change in exercise tolerance



Impact of cough



Frequency of NTM-LD exacerbations



Change in sputum production

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