



HHS Public Access

Author manuscript

Eur Respir J. Author manuscript; available in PMC 2019 July 27.

Published in final edited form as:

Eur Respir J. 2018 March ; 51(3): . doi:10.1183/13993003.00170-2018.

Treatment outcome definitions in nontuberculous mycobacterial pulmonary disease: an NTM-NET consensus statement

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Conflict of interest: E. Cambau has received non-financial support for travel from ESCMID, during the conduct of the study. C.L. Daley has received grants and personal fees from Insmad, outside the submitted work. C. Lange has received personal fees for independent lectures at sponsored symposia from Chiesi, Gilead, Abbvie, MSD, Becton Dickinson, Janssen, Lucane, Novartis and ThermoFisher, outside the submitted work. T.K. Marras has received grants from Insmad (site investigator for clinical trial, funds paid to institution), personal fees for consultancy (for designing clinical trials in NTM lung disease, with all funds paid to institution) from Insmad and RedHill, and personal fees from AstraZeneca (honoraria for CME on mycobacterial disease, funds paid to institution), outside the submitted work. K. Morimoto has received personal fees for consultancy from INSMED, outside the submitted work. K.N. Olivier received grants from Insmad Inc. and Matinas Biopharma, during the conduct of the study. R. Thomson received consultancy fees for work unrelated to this manuscript from Insmad and Savara.

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Introduction

Nontuberculous mycobacterial pulmonary diseases (NTM-PD) are increasingly recognised as opportunistic infections of humans. These chronic pulmonary infections have two main presentations. The first is a fibro-cavitary disease, that occurs in patients with pre-existing pulmonary diseases, such as chronic obstructive pulmonary disease, bronchiectasis, previous tuberculosis or other structural lung disease. The second presentation is a nodular-bronchiectatic disease of primarily the lingula and middle lobe that tends to affect a middle-aged and elderly female population [1].

Treatment of NTM-PD requires long-term administration of complex multidrug therapies that are species-specific. Currently recommended regimens are supported by a very limited evidence base [2, 3]. The increasing incidence of NTM-PD has sparked increased interest in performing prospective randomised clinical trials [4]. One of the drawbacks of the existing case series and clinical trials is that they have applied different outcome measures [5]. This hampers meta-analyses, which are important in these still understudied infectious diseases.

To enhance the quality and interpretability of the results of future trials and retrospective cohort studies, we aimed to formulate clear and broadly acceptable outcome definitions for NTM-PD treatment.

Methods

Critical outcome parameters were selected and their draft definitions were produced during two meetings (Copenhagen, April 2015; San Diego, October 2015) of the American Thoracic Society/European Respiratory Society/Infectious Diseases Society of America/European Society of Clinical Microbiology and Infectious Diseases committee writing the upcoming guidelines on diagnosis and treatment of NTM-PD, and during the 4th biannual NTM-NET meeting (Amsterdam, September 2015). During these meetings, present panel members were asked to formulate what they considered key outcome parameters that required definitions. Then, panel members were asked to come up with possible definitions and their potential limitations. The lead author (J. van Ingen) took notes during these meetings and selected the outcome parameters and prepared the first draft definitions from

these notes. Four additional experts within NTM-NET (T. Aksamit, W-J. Koh, K. Morimoto, R. Thomson) were then counselled to ensure a broader and geographically more diverse group.

A five-round revision and voting process was initiated, following previously used methodology [6]. The outcome definitions were developed in this stepwise mechanism:

Step 1:

Preliminary definitions, drafted by the lead author during the meetings, were shared with panel members, with an invitation to send in alternatives.

Step 2:

Alternative definitions were collected by the coordinating author.

Step 3:

All panel members and the additional NTM-NET experts were asked to select one preferred definition from those drafted in steps 1 and 2. The vote was blinded to all other participants.

Step 4:

For each definition, the one that received most votes was selected for inclusion in this statement.

Step 5:

All participants were asked to indicate their agreement or disagreement with the selected definition. Results of the decisions are indicated at the end of each definition.

All voting procedures were managed by the lead author (J. van Ingen) and performed by e-mail, with ballots prepared using Microsoft Excel software. All votes were counted independently by lead and senior authors (J. van Ingen, D. Wagner). Definitions were accepted if agreement of >80% of the participants was reached.

Results

23 NTM-NET members participated in writing this statement. For each parameter, the complete list of possible definitions sent out for voting in Step 3 is presented in table 1. The final definitions are presented in bold face in table 1, with the results of voting in step 4 and the extent of consensus achieved in step 5.

Discussion

To improve the quality in reporting and enable meta-analyses of clinical studies, we are now proposing consensus definitions for key outcome parameters to be used in the treatment of NTM-PD. These definitions can also aid in the design of future clinical trials for new treatment regimens.

Consensus on the definition for cure proved hardest to obtain due to the risk of reinfection in patients with NTM-PD. For other diseases, including tuberculosis (TB), the term “cure” is reserved for patients remaining disease-free for a specified period after the end of treatment [6, 7]. For NTM this is more complicated; (clinical) cure is based on a decrease in, rather than full resolution of, symptoms, because of underlying lung diseases and exposure to the causative agents is likely commonplace owing to their ubiquity in the environment [1, 2]. Typing tools to distinguish relapses from reinfections and thus to offer feedback on treatment effect are not widely available yet and have not been standardised and validated [8]. Hence, for now, adding a disease-free period after treatment cessation to define cure did not obtain a majority of expert votes. Aware of this limitation, we propose to use the end of treatment as the moment to define cure. In the future, with validated biomarkers of disease and tools for strain typing, the definition of cure may include a period of disease-free survival with negative cultures.

There was very high agreement for definitions other than for cure, although the vote in step 3 did not always yield a clear favourite. Some draft definitions varied only in details (*e.g.* one or two positive cultures; table 1); in absence of any evidence in favour of either option, having agreed-upon definitions was perhaps considered as important as their exact details.

Applying these definitions, a single positive culture after culture conversion does not yet mean treatment failure. This stresses the importance of requesting repeated follow-up cultures after culture conversion and end of treatment. Sputum induction or bronchoscopy, perhaps with computed tomography imaging for guidance, may be required to obtain good quality respiratory specimens to determine treatment outcome. Essentially, a single positive culture after culture conversion equals that of a single positive culture at the time of first diagnosis [2].

The next challenge is how to convert these definitions into uniform clinical practice. A pressing issue is what to do when patients meet the definition for failure. Is that the point when a switch to a second-line regimen is warranted? The timing set out in the current definition, after 12 months of treatment, may be regarded by some to be too conservative. One may question whether it is ethical to wait that long in patients still culture positive after 6 months of guideline-compliant NTM-PD treatment. In addition, this timing aspect may be different for disease caused by different NTM species or for different disease manifestations, *i.e.* fibro-cavitary disease versus nodular-bronchiectatic disease. In multidrug-resistant TB, a manifestation of TB that shares similar features to NTM-PD in respect to management, adverse events of therapy, prognosis and costs, a positive culture status at 6 months of therapy has recently been suggested to define failure [9]. The recent study on semi-quantitative cultures to monitor treatment effect suggests that a lack of microbiological response after 6 months of treatment is a very accurate predictor of treatment failure (non-response) at 12 months and beyond [10], and this time point has thus been chosen in ongoing clinical trials in failing patients [4]; on the other hand, culture conversion after month 6 certainly does occur [11, 12].

Proper use of these outcome definitions does set requirements for standards of care for NTM-PD patients. For example, to effectively monitor culture conversion and

(microbiological) cure requires submission of multiple good-quality sputum samples, but may also require computed tomography (CT) imaging and guided bronchoscopy for bronchoalveolar lavage (BAL) specimens, at set times during and after the entire course of treatment. Also, monitoring improvement in symptoms and signs to establish clinical cure requires the use of validated instruments to measure these. The recent recommendations on diagnosis and treatment of NTM-PD in cystic fibrosis patients provide pragmatic schemes to set these standards [3]. Nonetheless, standards of care specific to NTM-PD and relevant to all patients would still be helpful.

These definitions and the process by which they were set have some important limitations. First, these definitions result from a debate that included expert pulmonologists, infectious disease physicians, microbiologists and a patient representative. Thus, the process and its outcomes are based on expert opinion rather than a systematic review of the literature, a shortcoming also noted for the TB-NET document [4] from which the methodology was derived [13]. This methodology was chosen for its pragmatism, in a field devoid of data to support weighing of relevance of outcomes based on systematic review. This method also introduces selection bias as most members of this NTM-NET committee are in frequent contact and this may have already introduced uniformity in the definition and use of outcome parameters; also, four panel members joined after the initial drafting, hence could only vote, not draft. Second, these outcome definitions reflect the outcomes of current treatment regimens. With the advent of new treatment modalities for NTM-PD, including new antibiotics, time to sputum culture conversion may be shortened and this could affect the definition of treatment failure. Third, in the absence of other validated biomarkers for treatment response, these definitions rely heavily on culture of respiratory specimens. This is problematic in patients who do not produce sputum and may require CT imaging, guided bronchoscopy and the acquisition of BAL fluid specimens to determine culture conversion and cure, as stated in the recent British Thoracic Society guidelines on NTM-PD management [14]. Non-culture-based biomarkers for diagnosis and treatment response remain urgently needed. Radiological improvement as a marker is helpful but does not, by definition, follow the clinical and microbiological response to treatment [15, 16]. Fourth, molecular detection of NTM directly in clinical specimens is still not commonplace, but is likely to become routine in the upcoming years [17]. The interpretation of its results and how these affect current outcome definitions should be subject of future studies. Last, for many (especially retrospective) studies, the data gathered will not allow use of all outcomes defined here. For example, the distinction of recurrences into relapses and reinfections requires molecular typing data.

In summary, we have achieved international expert consensus on treatment outcome definitions for NTM-PD, using a five-round drafting and voting process. There was very high agreement among experts for all outcome definitions with the exception of the definition for cure. Definitions will need to be re-evaluated when more longitudinal clinical data on NTM-PD become available. We encourage the application of these definitions in both clinical management and in future studies and their design. Uniform outcome measures and reports will facilitate meta-analyses of trials and case series, which in turn will increase the quality of evidence available to support treatment regimens for these difficult-to-treat infections.

Acknowledgements

The authors wish to thank the American Thoracic Society, European Respiratory Society, Infectious Diseases Society of America and European Society of Clinical Microbiology and Infectious Diseases for organising the two meetings during which the process leading to this statement was initiated. These organisations do not officially endorse this NTM-NET consensus statement.

Support statement: Funded in part by the Division of Intramural Research, National Heart, Lung and Blood Institute, NIH. J. van Ingen is supported by a personal grant from the Netherlands Organization for Scientific Research NWO/ ZonMW (Veni 016.176.024).

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TABLE 1

List of definitions

Version #	Outcome parameter	Votes [¶]	Agreed ⁺
Culture conversion			
1	The finding of at least two consecutive negative mycobacterial cultures from respiratory samples during antimycobacterial treatment (the sampling date of the first negative culture is then the date of culture conversion)	0	
2	The finding of at least two consecutive negative mycobacterial cultures from respiratory samples, <u>collected at least 4 weeks apart</u> , during antimycobacterial treatment (the sampling date of the first negative culture is then the date of culture conversion)	6	
3	The finding of at least two consecutive negative mycobacterial cultures from respiratory samples, <u>collected at least a day apart</u> , during antimycobacterial treatment (the sampling date of the first negative culture is then the date of culture conversion)	2	
4	The finding of at least <u>three</u> consecutive negative mycobacterial cultures from respiratory samples during antimycobacterial treatment (the sampling date of the first negative culture is then the date of culture conversion)	6	
5	<i>The finding of at least <u>three</u> consecutive negative mycobacterial cultures from respiratory samples, collected at least 4 weeks apart, during antimycobacterial treatment (the sampling date of the first negative culture is then the date of culture conversion)</i>	9	22/23 (96%)
Microbiological cure			
1	<i>Finding multiple consecutive negative but no positive cultures with the causative species from respiratory samples after culture conversion and until the end of antimycobacterial treatment</i>	9	22/23 (96%)
2	Finding multiple consecutive negative but no positive cultures with the causative species from respiratory samples after culture conversion <u>and at the end</u> of antimycobacterial treatment	6	
3	Permanent culture conversion that is maintained after therapy cessation	8	
Cure			
1	Antimycobacterial treatment completed, with documented culture conversion and without any evidence of failure or recurrence until 24 months after the end of antibiotic treatment	3	
2	Negative culture status 6 months after treatment initiation, no positive culture thereafter and being relapse-free 1 year after treatment completion	3	
3	<i>Antimycobacterial treatment completed, with fulfilment of criteria for both microbiological and clinical cure</i>	17	19/23 (83%)
Clinical cure			
1	<i>Patient-reported and/or objective improvement of symptoms during antimycobacterial treatment, sustained until at least the end of treatment, but no cultures available to prove culture conversion or microbiological cure</i>	11	21/23 (91%)
2	Patient-reported and/or objective improvement of symptoms during antimycobacterial treatment, sustained until at least the end of treatment, but no cultures <u>obtainable</u> to prove culture conversion or microbiological cure	3	
3	Patient-reported and/or objective improvement of symptoms during antimycobacterial treatment, sustained <u>until at least 24 months after</u> the end of antibiotic treatment	7	
4	Patient-reported and/or objective <u>resolution of signs and symptoms</u> during antimycobacterial treatment, sustained until at least the end of treatment, but no cultures available to prove culture conversion or microbiological cure	2	
Treatment failure			
1	The re-emergence or persistence of positive cultures with the causative species from respiratory samples after ≥12 months of antimycobacterial treatment, while the patient is still on treatment	6	
2	<i>The re-emergence of <u>multiple positive cultures</u> or persistence of positive cultures with the causative species from respiratory samples after ≥12 months of antimycobacterial treatment, while the patient is still on treatment</i>	14	23/23
3	Positive culture status 6 months after treatment initiation or thereafter or relapse within 1 year after treatment completion	3	
Recurrence			

Version #	Outcome parameter	Votes [#]	Agreed ⁺
1	The re-emergence of positive cultures with the causative species from respiratory samples within 24 months after cessation of antimycobacterial treatment	3	
2	<i>The re-emergence of at least two positive cultures with the causative species from respiratory samples after cessation of antimycobacterial treatment</i>	15	21/23 (91%)
3	The re-emergence of positive cultures with the causative species from respiratory samples after cessation of antimycobacterial treatment	5	
	Relapse		
1	The emergence of multiple positive cultures with the same strain of the causative species after treatment	3	
2	<i>The emergence of at least two positive cultures with the same strain of the causative species after the end of treatment</i>	11	21/23 (91%)
3	Do not use this as an outcome (because infections may be polyclonal hampering same/new classification and/or poorly standardised typing methods)	9	
	Reinfection		
1	The emergence of multiple positive cultures with a different strain of the causative species or a strain of a different species during treatment or after treatment	6	
2	<i>The emergence of at least two positive cultures with a different strain of the causative species or a strain of a different species after the initiation of the treatment episode</i>	10	23/23
3	Do not use this as an outcome (because infections may be polyclonal hampering same/new classification and/or poorly standardised typing methods)	7	
	Died		
1	<i>Death due to any reason, but during NTM-PD treatment</i>	15	22/23 (96%)
2	Death during observation	8	
	Unknown outcome		
1	<i>Patient is no longer seen by his/her treating physician, so follow-up of treatment outcome is not possible (umbrella term for “lost to follow-up” and “transfer out”)</i>	17	23/23
2	Outcome not assessed (transferred out, no culture status at months while being in care or no post-treatment 6 assessment)	6	
	Died due to NTM-PD		
1	<i>All causes of death that would not have occurred if the patient had not had pulmonary NTM disease</i>	12	22/23 (96%)
2	Do not use this as an outcome - too hard to determine causality/relation	11	
	Treatment halted		
1	<i>Physician- or patient-initiated pre-term cessation of antimycobacterial treatment</i>	23	23/23

Bold italic font indicates definitions that received the most votes in round 3. Underlined sections emphasise differences between statements.

[#]: version of the definition suggested in round 3 of the voting process

[#]: number of votes received from the 23 voters in round 3

⁺: level of agreement obtained among 23 voters in round 5. NTM-PD: nontuberculous mycobacterial pulmonary disease.