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Variable agreement among experts regarding *Mycobacterium avium* complex lung disease

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Abstract

Data regarding many clinical aspects of pulmonary *Mycobacterium avium* complex (pMAC) are lacking. Guidelines rely substantially upon expert opinion, integrated through face-to-face meetings, variably weighting individual opinions. We surveyed North American non-tuberculous mycobacteria experts regarding clinical aspects of pMAC using Delphi methods. Nineteen of 26 invited experts (73%) responded, with extensive variability. Convergence could not be reached for most questions. Respondents described extensive uncertainty around specific issues. Findings underscore urgent need for more research.

Keywords

Delphi technique; *Mycobacterium avium*-intracellulare infection; mycobacterium infection; non-tuberculous mycobacterium; practice guideline

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Non-tuberculous mycobacterial (NTM) lung disease is increasingly common, with prevalence estimates in the USA and Canada ranging 6.8–41.3/100 000 in the general population[1–4] and 20–>200/100 000 in elders.[1–3,5] Pulmonary *Mycobacterium avium* complex (pMAC) disease comprises the bulk of NTM disease, with recent North American annual increases of 2.6–8.5%.[3,5,6] pMAC disease is a challenging clinical problem. Diagnostically, it requires clinical, radiological and microbiological data.[7] Therapeutically, prolonged courses of multiple antibiotics are often required,[7] with high rates of drug toxicity,[8] and inadequate success rates.[9] Finally, there is considerable financial burden.[10–12] Comprehensive data regarding many clinical aspects of pMAC are lacking. Guidelines rely substantially upon expert opinion, integrated through meetings and discussions,[7] generating variably weighted individual opinions, not necessarily reflecting reality.[13] We sought to identify objective collaborative estimates and opinions regarding selected clinical aspects of pMAC.

Herein ‘pMAC’ indicates MAC isolation from the lungs, and ‘pMAC disease’ indicates MAC lung disease, as defined by American Thoracic Society criteria.[7] The University Health Network Research Ethics Board approved the study (09–0640-AE), waiving the need for informed consent. We identified pMAC experts as co-authors of current NTM guidelines[7] or attending physicians from a group of recognized NTM centres in the USA or Canada. Participants were surveyed by email, regarding epidemiology, treatment and estimates regarding outcomes and prognosis, and asked to provide confidence levels (low, medium, high) for responses. Because of differences in prognosis and treatment response between patients with different clinical characteristics, surveys referred to patients with pMAC without underlying lung disease or immune suppression. For collaborative integration of responses between participants, a Delphi process of sequential survey iterations was employed. Successive iterations included aggregate results from the prior iteration, which participants were encouraged to consider in their responses. Iterations wereperformed until either target ranges were reached, or until there was no convergence in two successive iterations. Target ranges were: proportions ±0.1; time to diagnosis ±1 year; treatment duration ±3 months; time to recurrence ±6 months; and median survival ±2.5 years. For treatment preference questions, there was only one attempt at convergence (assuming substantial treatment variability, and that two iterations provide adequate reflection upon personal practice and treatment beliefs). To explore participants’ opinions, comments were encouraged. Comments from the first iteration were grouped according to common themes.

Nineteen of 26 (73%) invited experts took part. Participants were from 10 centres (nine USA, one Canada); 47% (9/19) were NTM guideline authors, 74% (14/19) were pulmonary physicians and 26% (5/19) were infectious diseases physicians. Table 1 presents the summary of responses. Significant variability was observed between participants in the initial survey iteration, with wide ranges for estimates of the proportions of patients: with MAC isolated from the sputum who have pMAC disease, in whom antimycobacterial agents are not initially prescribed, with spontaneous remission and with recurrence after successful therapy. Variability was also high regarding time to recurrence, treatment regimens after relapse, duration and success of less-intensive therapy (<3 drugs or short course(s) of

therapy) and, especially, survival. Moderate response variability was observed for the duration of intensive therapy and success of initial intensive therapy. Convergence to within the prespecified ranges was achieved for only two questions, with a lesser degree of convergence observed for most questions.

Confidence in responses was generally high for selected treatment strategy and duration, moderate for estimating the proportion of patients with disease, time to diagnosis, probability of treatment success and recurrence, and low for estimating survival and probability of spontaneous remission. For questions where participants expressed lower confidence, wider response ranges were observed. Comments were grouped according to themes, including ‘don’t know’ or ‘unsure’ (27 responses), less-intensive therapy is useful for disease suppression when patients are intolerant of intensive therapy and/or have incurable disease (24 responses), response variability due to variable patient features, including comorbidity and drug intolerance (19 responses), and referral bias as an important source of variability (16 responses).

In surveying pMAC disease experts, we noted substantial variability in many estimates, variable levels of confidence in responses, incomplete convergence in responses for most questions over survey iterations and a few common themes from participants’ comments. The substantial variability is not unexpected, with several possible contributing causes. First, polled NTM treatment centres have different underlying referral populations, so the mix of disease extent, age, comorbidities, prior treatment history and desire to pursue aggressive therapy may differ accordingly. Patient factors could lead to different treatment strategies and referral bias was frequently mentioned in participants’ comments. Second, limited data regarding optimal drug regimens, natural history and survival undoubtedly contribute to estimate variability. Finally, variable opinions and practice may result from challenges in pMAC disease management. Challenges like the inability to predict who requires therapy (vs simple observation), frequent drug intolerance and inadequate long term outcomes probably direct physicians to develop different clinical strategies regarding drug combinations, doses and schedules, as well as ancillary approaches to reduce drug toxicities and improve clinical response. These challenges could magnify treatment variability to levels far greater than in the setting of diseases with extensive data to guide management, perhaps elevating the importance of the clinician’s experience.[14]

The lack of convergence over survey iterations could also be due to a combination of differences in patients between participants and limited data regarding many aspects of pMAC. Clinical practice comprises some balance between ‘experience-based’ and ‘evidence-based’ medicine,[15] and a paucity of data likely tips the balance toward experience-based practice. In our study, the lack of convergence was probably related to such a phenomenon, where different experts, seeing different patient types, develop somewhat different clinical opinions. Regardless of cause, the lack of convergence for many clinical questions suggests that clinical guideline recommendations in this area may be driven primarily by dominant contributors, and the strength of recommendations will likely be relatively weak given the limited available data. Low participant confidence in responses further underscores the limitations imposed by the dearth of available data. Themes that emerged from participants’ comments provide insight into the state of knowledge in pMAC.

The need for more research is underscored by ‘don’t know’ or ‘unsure’ as the most common comment. A flexible approach to therapy and antimicrobial regimen selection was implied by comments regarding utility of less-intensive suppressive therapy in patients intolerant of intensive therapy and/or with incurable disease, highly variable patient features, and referral bias.

Recall and referral biases are limitations herein. Recall bias could be mitigated by reviewing patient records from participants’ clinics, but requisite resources were unavailable. We think it is doubtful that recall bias drove the main findings—substantial practice variability and clinical uncertainty. Referral bias could be mitigated by posing specific questions around hypothetical patients. This method would require very detailed patient descriptions to permit experts to provide specific answers, possibly reducing response rates. Further, such examples might inappropriately ignore many patient situations and over-simplify pMAC complexities.

The substantial variability of expert opinion around MAC lung disease highlights the overwhelming need for coordinated clinical research to better understand disease evolution, determinants of progression and treatment responsiveness, and prognosis. Equally necessary are more effective and better tolerated drugs for treating these infections. The current lack of clarifying research will continue to limit clinical guidelines quality and maintain substantial variability in expert opinion.

Abbreviations:

MAC	*Mycobacterium avium* complex
NTM	non-tuberculous mycobacteria
pMAC	pulmonary *Mycobacterium avium* complex (pMAC)
pNTM	pulmonary non-tuberculous mycobacteria

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Table 1

Summary of Delphi process regarding clinical aspects of MAC lung disease

	Iteration [number responded]					
	First				Final	
		Level of confidence				
Question	Median (interquartile range)	High	Med	Low	Median (interquartile range)	Convergence achieved?
What per cent of all people with ≥1 MAC isolate have disease?	50 40–75)% [*n* = 19]	28% [5/18]	61% [11/18]	11% [2/18]	50 40–65)% [*n* = 19]	No
What is the average duration from symptom onset, to diagnosis of disease?	2 1–5) years [*n* = 19]	28% [5/18]	61% [11/18]	11% [2/18]	2 2–3) years [*n* = 19]	No
In what percentage of new patients do you use:	[*n* = 19]	—	—	—	—	No
•Intensive therapy	79 70–85)%	63%	31%	6%	80 70–85)%	—
•Less-intensive therapy	6.25 1–10)%	[10/16]	[5/16]	[1/16]	5 1–10)%	—
•No antimycobacterials	10 5–28)%				10 10–25)%	—
Among new patients who are not treated with antimicrobial drugs:	—	—	—	—	—	—
•Proportion who spontaneously remit	10 5–20)% [*n* = 18]	24% [4/17]	29% [5/17]	47% [8/17]	10 5–10)% [*n* = 19]	Yes
•Median survival in untreated patients	12 5–15) years [*n* = 16]	6% [1/16]	13% [2/16]	81% [13/16]	10 10–12) years [*n* = 19]	No
Among patients treated with ‘intensive’ therapy:	—	—	—	—	—	—
•Duration of intensive therapy	18 15–18) months [*n* = 19]	67% [12/18]	33% [6/18]	0% [0/18]	18 17–18) months [*n* = 18]	Yes
•Success[†] of intensive therapy when tolerated)	72.5 70–80)% [*n* = 19]	28% [5/18]	67% [12/18]	5% [1/18]	70 70–75)% [*n* = 19]	No
Among patients successfully treated with ‘intensive’ therapy:	—	—	—	—	—	—
•Proportion who experience recurrence	30 20–50)% [*n* = 19]	33% [6/18]	50% [9/18]	17% [3/18]	30 25–45)% [*n* = 19]	No
•Time to recurrence	18 10–24) months [*n* = 19]	11% [2/18]	50% [9/18]	39% [7/18]	18 15–18) months [*n* = 19]	No
Treatment of relapse post successful intensive therapy	—	—	—	—	—	—
•Intensive therapy again	70 50–80)% [*n* = 19]	39% [7/18]	61% [11/18]	0% [0/18]	70 70–80)% [*n* = 19]	No
•Less-intensive therapy	10 1–20)% [*n* = 19]	56% [10/18]	39% [7/18]	6% [1/18]	10 7.5–15)% [*n* = 19]	No

Question	Iteration [number responded]					
	First				Final	
		Level of confidence				
	Median (interquartile range)	High	Med	Low	Median (interquartile range)	Convergence achieved?
•Median survival if recurs and not treated further	10 5–13.75) years [*n* = 17]	19% [3/16]	25% [4/16]	56% [9/16]	10 8–10) years [*n* = 19]	No
Among patients treated with less-intensive therapy	—	—	—	—	—	—
•Proportion controlled with less-intensive therapy	50 22.5–50)% [*n* = 17]	19% [3/16]	50% [8/16]	31% [5/16]	50 30–50)% [*n* = 19]	No
•Duration of less-intense therapy if successful)	17 12–24) months [*n* = 15]	43% [6/14]	29% [4/14]	29% [4/14]	18 15–21) months [*n* = 19]	No
•Proportion ‘cured’ with less-intensive therapy	20 7.5–50)% [*n* = 16]	21% [4/15]	33% [5/15]	40% [6/15]	20 15–30)% [*n* = 19]	No
Treatment of recurrence after less-intensive therapy	—	—	—	—	—	—
•Intensive therapy	60 35–77.5)% [*n* = 17]	21% [3/14]	64% [9/14]	14% [2/14]	50 50–67.5)% [*n* = 18]	No
•Less-intensive therapy again	30 7.5–50)% [*n* = 17]	Not done	Not done	Not done	46 32.5–50)% [*n* = 18]	No
Median survival when controlled with ongoing less-intensive therapy	10 8–12.25) years [*n* = 16]	20% [3/15]	40% [6/15]	40% [6/15]	10 10–10) years [*n* = 19]	No
Median survival when not controlled with less-intensive therapy and not treated further	4 3–10) years [*n* = 16]	0% [0/15]	40% [6/15]	60% [9/15]	5 5–6) years [*n* = 19]	No

[†]Success defined as resolution or control of symptoms.

MAC lung disease implies the absence of an obvious predisposing condition such as pre-existing structural lung disease or immune suppression. Disease refers to a significant lung infection with *Mycobacterium avium* complex, as defined by the American Thoracic Society 2007 NTM guidelines.[6] Intensive therapy—prolonged, multidrug, similar guidelines recommendations. Less-intensive therapy—<3 drugs or relatively short course(s) of therapy.

MAC, *Mycobacterium avium* complex.