Opinions Differ by Expertise in *Mycobacterium avium* Complex Disease

Theodore K. Marras^{1,2}, D. Rebecca Prevots³, Frances B. Jamieson^{2,4}, and Kevin L. Winthrop^{5,6}; on behalf of the Pulmonary MAC Outcomes Group*

¹Division of Respiriology, University Health Network and Mount Sinai Hospital, Toronto, Ontario, Canada; ²University of Toronto, Toronto, Ontario, Canada; ³National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; ⁴Public Health Ontario, Toronto, Ontario, Canada; ⁵Oregon Health and Science University, Portland, Oregon; and ⁶Portland Veteran's Affairs Medical Center, Portland, Oregon

Abstract

Rationale: Pulmonary *Mycobacterium avium* complex treatment guidelines rely largely on expert opinion. The extent to which nonexperts agree with recommendations of experts in this clinical area is unknown.

Objectives: We sought to compare practices and perceptions of prognosis between experts and nonexperts.

Methods: We surveyed respirologists (Ontario, Canada, "nonexperts") and experts from nontuberculous mycobacterial disease centers of excellence (Canada and United States).

Measurements and Main Results: Forty-six Ontario respirologists (29% of 160) and 19 experts (73% of 26) participated. There was agreement between nonexperts and experts regarding disease duration before diagnosis (2 yr), likelihood of spontaneous remission (7–15%), typical duration of treatment (18 mo), first choice of therapy (guideline regimens), a subgroup of patients for whom less-intensive regimens are

avored (10% after recurrence), likelihood of recurrence (30%), and median survival (10 yr in most patients). Noted differences were that nonexperts estimated fewer patients with a positive culture had disease (30% vs. 50%, $P = 0.02$), used intensive guidelines therapy less often in new cases (50% vs. 79%, $P = 0.02$), and perceived a slightly lower success rate with guidelines therapy (65% vs. 75%, $P = 0.047$). Response ranges were wider for nonexperts, significantly so for selection of intensive guidelines therapy in new ($P = 0.01$) and recurrent ($P = 0.04$) cases.

Conclusion: Experts and nonexperts agreed on many issues. However, nonexperts perceived lower rates of disease among patients with isolates, tended to use less aggressive treatment approaches, and perceived lower success rates. Significant variability was observed in responses—often wider among nonexperts. Although these results are likely biased by referral, they may identify important areas for targeted education.

Keywords: *Mycobacterium avium-intracellulare* infection; *Mycobacterium* infections, nontuberculous; nontuberculous mycobacteria; practice guidelines

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*A complete list of members may be found before the beginning of the REFERENCES.

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Correspondence and requests for reprints should be addressed to Theodore K. Marras, M.D., Toronto Western Hospital, 7E-452, 399 Bathurst Street, Toronto, ON, M5T 2S8 Canada. E-mail: ted.marras@uhn.ca

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Pulmonary nontuberculous mycobacterial lung disease is increasingly common in Canada (1) and the United States (2–4).

Prevalence estimates range from 6.8 to 8.2 per 100,000 in the general population (1–3) and 20 to more than 100 per 100,000 in

older people (1–4). Pulmonary *Mycobacterium avium* complex disease composes the bulk of nontuberculous

mycobacterial disease, with recent annual increases in Canada and the United States of 2.6 to 8.5% (3–5). Pulmonary *M. avium* complex disease is a vexing clinical problem. The diagnosis is often challenging, requiring consistent clinical and radiologic evidence of disease in addition to microbiologic evidence (two or more sputum isolates or a single bronchoscopic isolate) (6). Multiple positive samples increase the likelihood of a diagnosis reflecting significant infection rather than sample contamination or transient colonization. Relatively low success rates (7) and high rates of drug toxicity with standard therapy create bigger challenges, making the decision to treat difficult, demanding careful consideration of potential benefits and risks of therapy. Once treatment is initiated, adjustment of the regimen is often required to improve tolerability or antimicrobial effect (8), and treatment requires multiple antibiotics for more than a year, with considerable costs to patients and health-care systems (9, 10). Recognizing these challenges, experts developed guidelines, combining available data and opinion, to assist clinicians (6).

The opinions of experts and generalist clinicians may differ, and the “correct” opinion may not be easily discerned. Considering relative experience, one assumes that experts’ opinions tend to be more often correct. However, in the context of clinical experience and referral biases, understanding differences in opinions is more difficult and underscores the need to carefully contextualize expert opinion. There are few data comparing expert and nonexpert physicians’ opinions in any field, and to our knowledge this has never been done regarding pulmonary *M. avium* complex. Knowledge of the presence of differences in opinions would be the first step in understanding the adequacy of guidelines’ content and likelihood of acceptance. We sought to investigate differences in opinion between pulmonary *M. avium* complex experts and practicing respirologists regarding selected aspects of natural history and treatment of this disease.

Methods

The University Health Network Research Ethics Board approved the study (09-0640-AE), waiving the need for informed consent.

We invited all practicing pulmonary physician (respirologist) members of the Ontario Thoracic Society (Canada) to complete a one-time, internet-based, anonymized survey regarding therapy and prognosis in pulmonary *M. avium* complex in 2010 (summarized in Table 1). Invitations were distributed by e-mail, with a single reminder after approximately 4 weeks. Experts were identified if they had coauthored the current American Thoracic Society nontuberculous mycobacterial guidelines (6) or were attending physicians at one of a selected group of recognized nontuberculous mycobacterial programs of excellence in the United States or Canada. Experts were invited to complete the survey to assess for differences in opinions with general respirologists and participate in an ongoing study seeking to reach consensus regarding management and prognosis (reported elsewhere). Experts who agreed to participate were surveyed by e-mail. Both surveys included questions regarding epidemiology, preferred treatment strategies, and estimates regarding clinical outcomes and prognosis. Experts were additionally asked to provide a level of confidence for each response (low, medium, high). Because of differences in prognosis and treatment response between patients with different clinical characteristics (especially lung cavitation and underlying lung disease), surveys referred to patients with pulmonary *M. avium* complex without underlying lung disease or immune suppression. Antimicrobial drug treatment was defined in the survey as intensive (three or more drugs, until ≥ 12 mo of culture-negative sputum, as recommended in guidelines) or less intensive (fewer than three drugs or relatively short courses of therapy, less intensive than recommended in guidelines). Our survey was not designed to test respondents’ knowledge *per se*, in that the “correct” answers are not necessarily known. We were interested in comparing the opinions of the two physician groups and acquiring insights from their differing perspectives. *Post hoc* analyses, comparing responses between subgroups of respondents, were also performed. To explore for bias by specialty, we repeated our analyses, comparing nonexperts versus experts but excluding the infectious diseases physicians. To explore for differences stemming from health-care systems (Canada vs. United States) we compared

responses between Canadian experts and U.S. experts.

Results are expressed as medians (quartiles); comparisons of central tendency used Wilcoxon rank-sum tests, and comparisons of variance were made using Conover scores. *P* values less than 0.05 were considered statistically significant. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Forty-six of an estimated 160 (29%) practicing respirologist members of the Ontario Thoracic Society responded to the survey (denominator estimated because record of precise number of members in active practice is not maintained). Most respondents (35 of 46, 76%) were in nonacademic practice. Their median (quartiles) time from certification was 17 (10–26) years, and they reported spending a median (quartiles) of 2.5 (1.5–4) days per week in a chest clinic. We asked how many patients with pulmonary *M. avium* complex the respondents had ever followed personally for 2 or more years. Twenty-eight percent had followed fewer than 5 patients, 35% had followed 5 to 10 patients, 20% had followed 11 to 20 patients, and 17% had followed more than 20 patients. We invited 26 pulmonary experts from 11 centers, and 19 of 26 (73%) took part. Participants were from 10 centers (nine United States, one Canada), and 47% (9 of 19) were nontuberculous mycobacterial guideline authors. Among experts’ subspecialty, 74% (14 of 19) were pulmonary, and 26% (5 of 19) were infectious diseases.

Table 1 presents the summary of responses. Significant response variability was observed between physicians within each group. Among nonexperts, the interquartile range was wide for the estimate of the proportion of patients with a sputum isolate who have disease (20–75%; median, 30%; *n* = 45). Choice of treatment strategy also varied among nonexperts. The interquartile ranges for using intensive therapy (three or more drugs, until ≥ 12 mo of culture-negative sputum, as recommended in guidelines) were wide in the setting of newly diagnosed disease (20–75%; median, 50%; *n* = 43) and recurrent disease after prior intensive (20–75%; median, 50%; *n* = 29) or less-intensive

Table 1. Summary of survey regarding pulmonary *Mycobacterium avium* complex disease, comparing responses between Ontario respirologists and experts

Question	Ontario Respirologists (N = 46)	Experts (N = 19)	P Value
What percent of all people with ≥ 1 pulmonary isolate have disease?	30 (20–75) %	50 (40–75) %	0.02
What is the average duration from symptom onset to diagnosis of disease?	2 (2–3) yr	2 (1–5) yr	0.67
In what percentage of new cases of disease do you use:			
Intensive therapy	50 (20–75) %	79 (70–85) %	0.02
Less-intensive therapy	0.5 (0–20) %	5 (1–10) %	0.51
No antimycobacterials	37.5 (15–70) %	10 (5–28) %	0.01
Among patients with disease who are not treated with antimicrobial drugs:			
Proportion who spontaneously remit	15 (10–25) %	7.5 (5–20) %	0.23
Median survival in untreated patients	10 (5–15) yr	12 (5–15) yr	0.31
Regarding patients with disease treated with “intensive” therapy:			
Duration of intensive therapy	18 (14–18) mo	18 (15–18) mo	0.83
Success of intensive therapy (when tolerated)	65 (50–75) %	75 (70–80) %	0.047
Regarding patients with disease successfully treated with “intensive” therapy:			
Proportion who experience recurrence	30 (20–50) %	30 (20–50) %	1.0
Time to recurrence	18 (12–24) mo	18 (10–24) mo	0.62
Treatment of relapse post successful intensive therapy			
Intensive therapy again	50 (20–75) %	70 (50–80) %	0.06
Less-intensive therapy	10 (0–20) %	10 (1–20) %	0.45
Median survival if recurs and not treated further	7 (5–15) yr	10 (5–15) yr	0.56
Proportion controlled with less-intensive therapy	36.5 (15–50) %	50 (25–50) %	0.39
Duration of less-intensive therapy (if successful)	12 (6–15) mo	17 (12–24) mo	0.03
Proportion “cured” with less-intensive therapy	10 (2.5–22.5) %	20 (7.5–50) %	0.08
Treatment of recurrence after less-intensive therapy			
Intensive therapy	35 (10–55) %	60 (50–75) %	0.20
Less-intensive therapy	65 (45–90) %	30 (10–50) %	0.08
Median survival when controlled with ongoing less-intensive therapy	10 (5–15) yr	10 (8–12.5) yr	0.52
Median survival when not controlled with less-intensive therapy and not treated further	4.5 (3–10) yr	4 (3–10) yr	1.0

Data are presented as median (interquartile range). Pulmonary *Mycobacterium avium* complex disease herein implies pulmonary *M. avium* complex disease without an obvious predisposing condition such as preexisting structural lung disease or immune suppression. Disease refers to a significant lung infection with *M. avium* complex, as defined by the American Thoracic Society 2007 nontuberculous mycobacteria guidelines (6). Isolate refers to a respiratory isolate of *M. avium* complex. Intensive therapy = prolonged, multidrug, similar to guidelines recommendations. Less-intensive therapy = fewer than three drugs or relatively short course(s) of therapy (less intensive than recommended in guidelines).

(10–55%; median, 35%; n = 4) therapy. Similarly, interquartile ranges were wide for other treatment strategies, including observation alone, and the prescription of

less-intensive therapy. Responses regarding the success of intensive therapy varied moderately (quartiles, 50–75%; median, 65%; n = 41) among nonexperts.

There was also substantial variability in responses among experts. There was a wide interquartile range for experts' estimates of the proportion of patients with an isolate who have disease (40–75%; median, 50%; n = 19). Experts generally reported a medium level of confidence for this question. Regarding the choice of treatment strategy, there was moderate variability in experts' withholding antibacterials in new cases (quartiles, 5–28%; median, 10%; n = 19), and the use of intensive antibiotic therapy for recurrent disease after prior intensive (quartiles, 50–80%; median, 70%; n = 19) or less-intensive (quartiles, 50–75%; median, 60%; n = 17) therapy, with generally high levels of confidence in their estimates. Finally, experts' estimates regarding the frequency of recurrence after successful intensive therapy were variable (quartiles, 20–50%; median, 30%; n = 19), without a dominant level of confidence for this question. Experts generally stated that their confidence was lowest for questions about survival and spontaneous remission, although the variance for responses to those questions did not seem to be very great.

Comparisons of responses between nonexperts and experts are presented in Table 1. Regarding epidemiology and natural history, experts believed that an isolate was significantly more likely to be associated with disease (50% vs. 30%, $P = 0.02$). However, estimates of time from symptom onset to diagnosis, probability of spontaneous remission, and median survival in untreated patients did not differ significantly between groups. Regarding approaches to therapy for new cases, experts would more often use intensive antibiotic therapy (79% vs. 50%, $P = 0.02$) and less often observe patients without antimycobacterial therapy (10% vs. 37.5%, $P = 0.01$). Experts also had a slightly more favorable estimate of treatment success (75% vs. 65%, $P = 0.047$). After successful treatment, both groups estimated an identical risk of recurrence and time to recurrence (30%, 18 mo). In the setting of recurrence, experts appeared to be slightly more likely to prescribe intensive therapy again (70% vs. 50%, $P = 0.06$), but the difference was not statistically significant. Both groups seemed to acknowledge less-intensive therapy as often beneficial in reducing symptoms but rarely curative.

We compared variances for the responses between the nonexperts and experts. Nonexperts' responses often

displayed greater variability regarding choice of therapy, with significantly greater variability observed for the selection of intensive therapy ($P = 0.01$) and simple observation ($P = 0.003$) in new cases and the selection of therapy in recurrences ($P = 0.04$).

In our *post hoc* analysis for bias by specialty (comparing nonexperts vs. experts but excluding the infectious diseases physicians [5 of 19 experts]), the results were almost identical, with no important differences. In the analysis exploring for differences arising from health-care systems (comparing responses between Canadian experts [$n = 4$] and U.S. experts [$n = 15$]), we did not identify important differences between these small groups.

Discussion

In our survey of respirologists in Ontario, Canada, and experts in pulmonary *M. avium* complex disease, we noted substantial agreement between the two physician groups. Nonexperts and experts agreed that the disease is usually present for years before diagnosis and rarely spontaneously resolves. There was further agreement that a typical treatment course is approximately 18 months, and although intensive treatment (as prescribed by guidelines) was the favored choice in both groups, both acknowledged that a less-intensive regimen may be used (and can be helpful) for some patients. Finally, both groups expected substantial recurrence rates and median survivals of approximately 10 years in most patients. These points of agreement could stem from either similar clinical experience or effective study of guidelines and other educational efforts by nonexperts, who have come to agree with positions proposed by experts.

We identified several interesting differences of opinion between groups. The experts: (1) perceive that people with sputum *M. avium* complex isolates more often have disease; (2) more often use intensive therapy (and less often observe without treatment); (3) estimate a slightly higher success rate with intensive therapy in new cases. Several factors likely contribute to these differences. Perhaps most influential is potential bias in patient populations who consult different groups of physicians. Patients consulting mycobacterial experts are probably more

likely to have established disease, are seeking intensive therapy, and are motivated to persevere through challenging drug regimens and multiple treatment modifications leading to clinical success. Physician differences are also undoubtedly important. Through extensive experience, experts may have acquired insights regarding the likelihood of disease among patients with *M. avium* complex isolates and expertise with tailoring drug regimens and adjuvant interventions (e.g., to reduce drug toxicities or augment mycobacterial eradication) to improve the likelihood of success. Experts likely have more enthusiasm for using intensive therapy that they have proposed in guidelines and believe to be helpful. The sampling of physicians (experts and nonexperts) also likely introduced bias. Nonexperts were all from Ontario, Canada, whereas experts were largely in the United States (15 of 19, 79%), so health-care system differences may contribute bias. Nonexperts were all respirologists, whereas experts included 26% (5 of 19) infectious diseases physicians. It may be that chest physicians and infectious diseases physicians approach the therapy of patients with pulmonary *M. avium* complex differently. However, in exploring for bias by specialty, we found nearly identical results after repeating our analyses with the infectious diseases physicians excluded. Nonexperts, although they represented a range of physicians regarding time since certification and experience with pulmonary *M. avium* complex, may not compose a representative sample of “nonexpert” pulmonary physicians across Canada and the United States, perhaps indicated by the response rate of 29%. Differences between Ontario and the expert centers’ proportion of *M. avium* complex, among pulmonary nontuberculous mycobacterial disease, might be relevant in explaining differences in responses. Site-specific data regarding mycobacterial species proportions among pulmonary nontuberculous mycobacterial cases at the expert centers are not available, so this issue cannot be accurately addressed. As a surrogate, recent studies in the United States and Canada, using variable methods, have estimated that 69 to 87.5% of pulmonary nontuberculous mycobacterial disease cases are *M. avium* complex (2, 3, 11–13). In Ontario, it is believed that 69% of pulmonary nontuberculous mycobacterial cases are *M. avium* complex (14). Perhaps

a relatively lower proportion of *M. avium* complex in Ontario is a contributing factor toward differing opinions between experts and nonexperts. A more direct comparison between experts and nonexperts could comprise sampling experts and nonexperts from the same geographic regions. This was not performed because of resource limitations but could be a focus of a future investigation.

Health-care system differences may also be a source of bias. However, as noted above, we could not identify differences stemming from health-care systems (Canada vs. United States), in that there were no important differences between Canadian experts ($n = 4$) and U.S. experts ($n = 15$), but we were limited by the small sample of Canadian experts. Finally, the accuracy of our instrument may be questioned due to the lack of extensive testing or the absence of case scenarios, but we do not think such limitations would differentially bias responses from either group of respondents.

Another interesting observation relates to the variability of responses within physician groups. Responses from both groups displayed significant variability, although somewhat more so from the nonexperts. An analogous observation has previously been described, when expert and general practicing gynecologists in North Carolina were provided scenarios regarding appropriateness of hysterectomy (15). There was significant disagreement within both groups, although less so among experts. This is not surprising, because experts are defined by extensive experience, implying a greater likelihood of providing accurate (and, as a group, precise) estimates regarding their specialty. Experts are also often defined in part by cooperative efforts to develop guidelines, a process that promotes convergence of opinion. It has been suggested that areas where experts agree, and nonexperts do not, may represent areas where expert-driven guidelines have the greatest impact (15). In the current study, most such instances were surrounding treatment choices. Although the choice of empiric antibiotic regimens is well described in guidelines (6), the skill, experience, and perseverance required to develop a regimen that is tolerable and ultimately effective may not be easily communicated in a guideline document. A question about what prompts referral to nontuberculous mycobacterial experts may

have provided further insight into areas where guidelines could be improved but unfortunately was not foreseen for the present study.

We compared respondents' answers with what we considered "best evidence," from original investigations and systematic reviews when possible, although this was difficult due to the paucity of data regarding many of the questions. Regarding clinical significance of one or more sputum isolates (experts, 50%; nonexperts, 30%), population-based studies from Ontario (1) and Oregon (2) suggest that 47 to 54% of such individuals are likely to have disease over a single year. The true value is likely higher, because some patients would undoubtedly have additional isolates in prior or subsequent calendar years and therefore would not be identified as having "disease" in single-year studies. Time from symptom onset to diagnosis was estimated at 2 years by both groups, but a prior study has suggested a much longer interval of 5 years (16), suggesting diagnosis is much slower than perceived by physicians who care for these patients. Median survival for most subsets of patients was estimated at approximately 10 years by both physician groups. Interestingly, a recent large study of mortality among patients with pulmonary *M. avium* complex at a single institution found a median survival of approximately 10 years as well (17). Regarding treatment success (experts, 75%; nonexperts, 65%), a systematic review has identified success rates with macrolide-based therapy of 56% (7). The discrepancy may relate to methodology. The systematic review included studies of less-intensive regimens and all types of patients and retained all patients for outcomes ascertainment, regardless of treatment completion. Our survey specified patients with idiopathic *M. avium* complex lung disease who tolerated and persisted with intensive therapy. Idiopathic disease (usually with "nodular bronchiectasis") likely responds better to therapy than disease in the context of underlying lung disease (more often

"fibrocavitary"). Alternatively, differences could also be related to an optimistic impression held by clinicians, analogous to consistently overestimating survival in terminally ill patients with cancer (18). Regarding recurrence of *M. avium* complex after successful treatment, both groups of physicians recognized this as commonplace and estimated the probability at 30%. Studies of this topic are often limited by short follow-up duration and ambiguous definitions of recurrence. Among three studies, a pooled rate of microbiologic recurrence after successful initial treatment, and follow-up of 36 to 72 months, can be calculated at 53 of 136 (39%) (8, 19, 20), perhaps very slightly different, reflecting definition of recurrence in most studies (microbiologic) or optimistic estimates from surveyed physicians.

We did not explicitly address the question regarding how closely clinicians actually follow the guidelines. The question would be of interest, help provide better focus on areas of discrepancy between experts and nonexperts, and assist in targeting guidelines' improvement and education. Because these patients are usually elderly with multiple comorbidities, and because the treatment is not nearly always effective, thoughtful judgment must be applied regarding the balance of benefits and risks of treatment. In this regard, the guidelines advise that less-intensive therapy is appropriate for some patients, therefore recommending intensive therapy (three or more drugs, ≥ 12 mo) for some patients and less intensive therapy for others. For this reason, we found it difficult to explicitly address whether physicians "follow guidelines," in that the intensity of therapy is only one of two components required (the other being patient factors) to objectively judge adherence to guidelines. As noted above, experts and nonexperts alike stated that intensive therapy was generally their first choice of therapy, but experts tend to use intensive therapy more frequently.

In summary, we observed that experts' and nonexperts' opinions align in many questions regarding the epidemiology, natural history, management, and outcomes of pulmonary *M. avium* complex. However, there was significant variability in the responses within both groups, and there were significant opinion differences between groups, with experts treating patients more intensively and estimating slightly greater treatment success. The results are probably biased by referral but identify potentially important differences that merit further investigation to facilitate targeted efforts at education to optimize care. Until better therapies become available, we think that emphasis should be placed on exploring the opportunity for optimizing the approach to combination antibiotic therapy for patients with pulmonary *M. avium* complex and maximizing information exchange with patients to enhance their understanding of the risks and benefits of therapy and maintain their position at the center of decision making. ■

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