Management of nontuberculous mycobacteria in lung transplant cases: an international Delphi study

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Shareable abstract (@ERSpublications)
Experts recommend performing sputum cultures and a chest CT scan for NTM screening in lung transplant candidates. They recommend against absolute contraindication to lung transplantation even with multiple positive sputum cultures for NTM. hiips://bit.ly/3WaSwLe

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Abstract

Rationale Nontuberculous mycobacterial (NTM) diseases are difficult-to-treat infections, especially in lung transplant (LTx) candidates. Currently, there is a paucity of recommendations on the management of NTM infections in LTx, focusing on *Mycobacterium avium* complex (MAC), *M. abscessus* and *M. kansasii*.

Methods Pulmonologists, infectious disease specialists, LTx surgeons and Delphi experts with expertise in NTM were recruited. A patient representative was also invited. Three questionnaires comprising questions with multiple response statements were distributed to panellists. Delphi methodology with a Likert scale of 11 points (5 to −5) was applied to define the agreement between experts. Responses from the first two questionnaires were collated to develop a final questionnaire. The consensus was described as a median rating >4 or <−4 indicating for or against the given statement. After the last round of questionnaires, a cumulative report was generated.

Results Panellists recommend performing sputum cultures and a chest computed tomography scan for NTM screening in LTx candidates. Panellists recommend against absolute contraindication to LTx even with multiple positive sputum cultures for MAC, *M. abscessus* or *M. kansasii*. Panellists recommend MAC patients on antimicrobial treatment and culture negative can be listed for LTx without further delay. Panellists recommend 6 months of culture-negative for *M. kansasii*, but 12 months of further treatment from the time of culture-negative for *M. abscessus* before listing for LTx.

Conclusion This NTM LTx study consensus statement provides essential recommendations for NTM management in LTx and can be utilised as an expert opinion while awaiting evidence-based contributions.

Introduction

Nontuberculous mycobacteria (NTM) comprise >200 species, some of which are opportunistic human pathogens. These mycobacteria are especially virulent due to their ability to survive intracellularly. They

can cause protracted disease requiring multidrug antimicrobial therapy with a high rate of recurrence and treatment failure [1, 2]. While NTM is implicated in many infections involving different systems, the lungs are the most frequent site of the disease [1, 3]. In the USA, NTM species most frequently isolated in pulmonary disease include *Mycobacterium avium* complex (MAC), *M. abscessus* and *M. kansasii* with an annual burden of ∼84 000 cases and an estimated prevalence of 12–17 per 100 000 [4–10]. Among all organ transplants, lung transplant (LTx) recipients have the highest risk of post-transplant NTM infection, with incidence ranging between 0.46 and 4.4% [11, 12]. LTx candidates, because of their underlying structural disease, are at increased risk of pre-transplant NTM colonisation and infection, which may predispose them to NTM infection after transplant in the presence of an immunosuppression [13]. There is no consensus on the management of NTM disease in the pre-transplant or post-transplant stages. This Delphi study was conducted to develop expert consensus on NTM management in the LTx population while awaiting clinical evidence-based guidelines.

Methods

A modified Delphi process was used for this study (figure 1). The Delphi process, first described by Delbecq and colleagues in the 1950s, uses a sequence of structured questionnaires to identify and build consensus on problems in the social sciences [14]. Medicine has been widely used to develop consensus recommendations on clinical questions when clinical evidence is unavailable [15–18]. Several sets of consensus studies in pulmonology have been based on the Delphi methods [19–25].

Physicians with significant clinical experience related to NTM (NTM experts) and LTx (LTx pulmonologists and surgeons) were invited to participate. Experts were selected based on having publications on NTM and NTM in lung transplants. 18 experts from 17 institutes and six countries with expertise in transplant pulmonology, cardiothoracic surgery and infectious diseases agreed to participate in this study. A patient representative was also included in the study. He is an NTM patient who underwent a successful lung transplant. The patient representative helped in improving the design of the study. The first questionnaire was drafted with statements categorised into segments, including NTM management protocols in LTx centres, diagnostics policies, LTx listing criteria in the context of NTM infections, preventive measures, post-transplant surveillance policies, pre- and post-transplant antibiotic therapy, suppressive antibiotic therapy, adjuvant therapy and the role of reduction in immunosuppression during NTM management. The statements were focused on MAC, *M. abscessus* and *M. kansasii*. Panellists used a

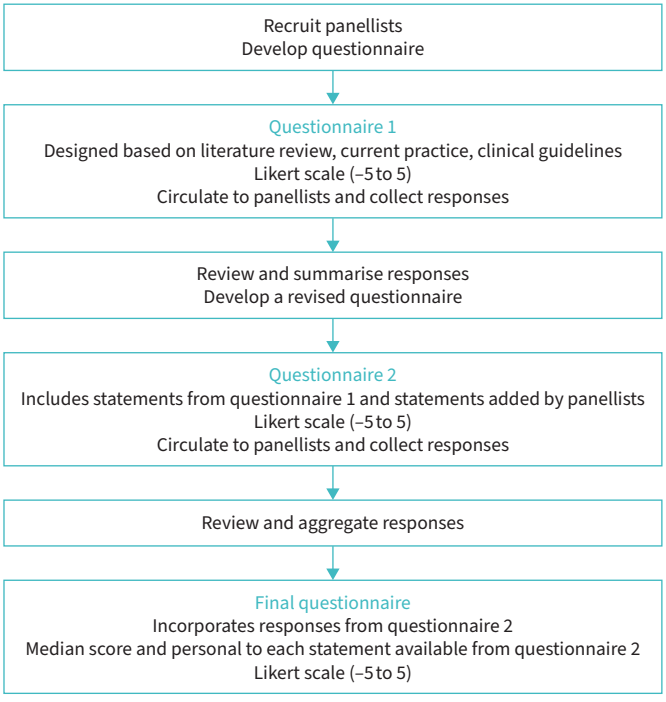

FIGURE 1 Structure of the nontuberculous mycobacteria lung transplant Delphi study.

Likert scale of 11 points to rate each piece of information, ranging from 5 to −5, representing strong agreement and strong disagreement, respectively. Antibiotics were individually ordered and were not presented as combination antibiotic regimens. Panellists were also able to add free-text comments. The first questionnaire responses were collated to create a second questionnaire, and statements were modified based on free-text comments. The final questionnaire was personalised to each panellist and included unchanged statements from the second questionnaire, the median rating from the entire panel and the individual panellist rating. Panellists could keep their rating or change it based on the median rating. The consensus was defined as a median of ⩾4 and ⩽−4.

Supplementary table S3 demonstrates our expert group characteristics including country.

Results

The final questionnaire included 69 questions with 726 responses. The consensus was reached on 197 responses. Results are reported as median (interquartile range). Figures 2 to 5 and supplementary tables S1 and S2 include the most significant statements of our study. Table 1 demonstrates our major recommendations in a summarised format.

NTM management protocol in LTx centres

58% of panellists have a set protocol for pre-transplant and post-transplant NTM screening.

Pre-transplant NTM screening in candidates and donors

Panellists agreed to utilise chest computed tomography (CT) scan (4 (2.5–5)) and sputum culture (5 (3.5–5)) for testing in LTx candidates. For NTM screening in LTx donors, panellists agreed to use bronchial washing acid-fast bacilli (AFB) smear and culture (4.5 (3–5)) and disagreed on not having any specific screening test (−4 (−5 to −0.75)).

Panellists agreed to screen every pre-transplant candidate regardless of risk factors (5 (4.75−5)). The consensus was reached for NTM culture and susceptibility to send sputum/bronchoalveolar lavage (BAL) cultures to reference labs for identification and susceptibility testing (5 (5–5)).

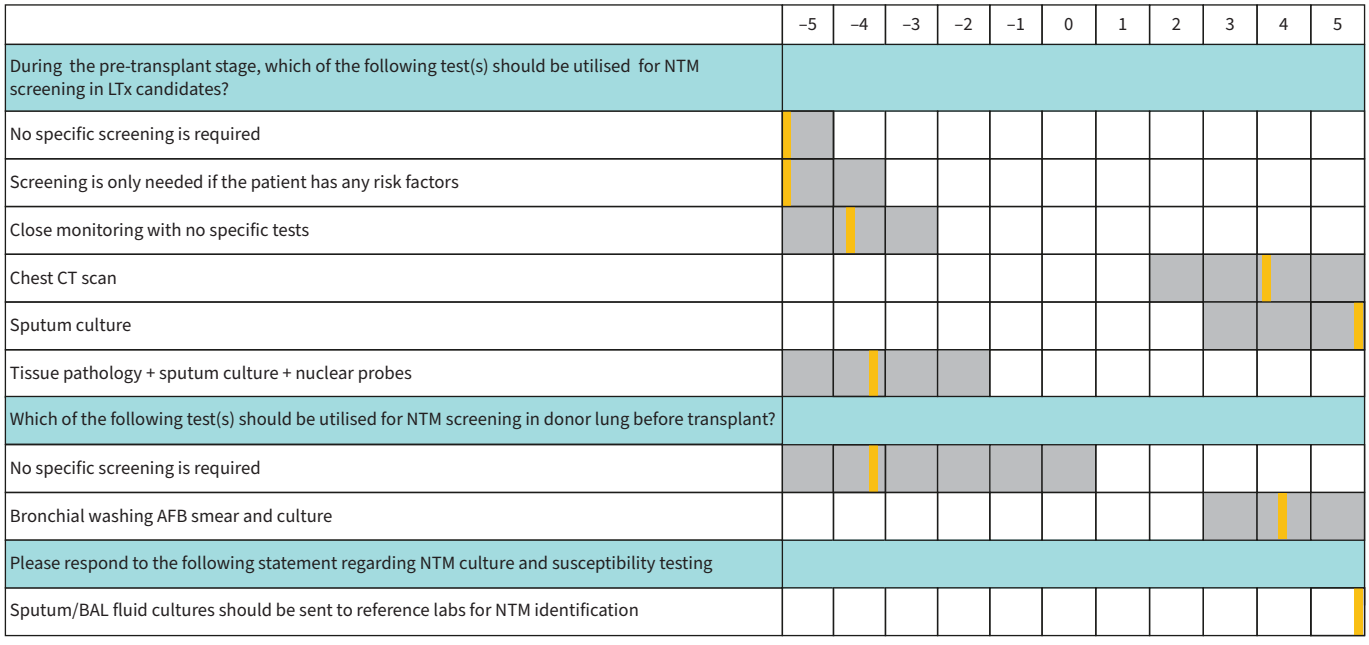

FIGURE 2 Summary of consensus on statements addressing diagnostic modalities for pre-transplant nontuberculous mycobacteria (NTM) pulmonary disease. The grey and orange colours represent the range and median on a Likert scale of 11 points (5 to −5). A median rating >4 or <−4 indicates for or against the given statement, respectively. LTx: lung transplant; CT: computed tomography; AFB: acid-fast bacilli; BAL: bronchoalveolar lavage.

	−5	−4	−3	−2	−1	0	1	2	3	4	5
During the pre-transplant stage, patients with MAC infection who are currently on treatment and sputum culture-negative can be listed for LTx if:											
Patient can be listed for LTx without further wait if current status of sputum culture is negative											
LTx is contraindicated in these patients irrespective of culture status											
Sputum culture has been negative for past 6 months											
Sputum culture has been negative for past 12 months											
During the pre-transplant stage, patients with *M. abscessus* infection who are currently on treatment and sputum culture-negative can be listed for LTx if:											
LTx is contraindicated in these patients irrespective of culture status											
Sputum culture has been negative for past 12 months											
During the pre-transplant stage, patients with *M. kansasii* infection who are currently on treatment and sputum culture-negative can be listed for LTx if:											
LTx is contraindicated in these patients irrespective of culture status											
Sputum culture has been negative for past 6 months											
Sputum culture has been negative for past 12 months											
During the pre-transplant stage, patients with a history of treated MAC infection, currently not on treatment and sputum culture-negative, should be listed for LTx if:											
LTx is contraindicated irrespective of culture status											
Treated for MAC 12 months ago											
During the pre-transplant stage, patients with a history of treated *M. abscessus* infection, currently not on treatment and sputum culture-negative, should be listed for LTx if:											
LTx is contraindicated irrespective of culture status											
Treated for *M. abscessus* 12 months ago											
During the pre-transplant stage, patients with a history of treated *M. kansasii* infection, currently not on treatment and sputum culture-negative, should be listed for LTx if:											
LTx is contraindicated irrespective of culture status											
Treated for *M. kansasii* 6 months ago											
In patients with past history of *M. abscessus* infection and currently negative sputum culture, who are candidates for single LTx, what strategy do you follow to prevent NTM infection in allograft?											
Perform bilateral LTx											
Proceed with single LTx and wash the remaining native lung with amikacin											
History of *M. abscessus* infection is contraindicated in single LTx candidates											
Initiate and continue antibiotics for 12 months after transplant											
Initiate and continue antibiotics for 24 months after transplant											
In patients with past history of *M. kansasii* infection and currently negative sputum culture, who are candidates for single LTx, what strategy do you follow to prevent NTM infection in allograft?											
Perform bilateral LTx											
Proceed with single LTx and wash the remaining native lung with amikacin											
History of *M. kansasii* infection is contraindicated in single LTx candidates											
Initiate and continue antibiotics for 12 months after transplant											
Initiate and continue antibiotics for 24 months after transplant											

FIGURE 3 Summary of consensus on statements addressing transplant listing criteria in patients with nontuberculous mycobacteria (NTM) pulmonary disease. The grey and orange colours represent the range and median on a Likert scale of 11 points (5 to −5). A median rating >4 or <−4 indicates for or against the given statement, respectively. MAC: *Mycobacterium avium* complex; LTx: lung transplant.

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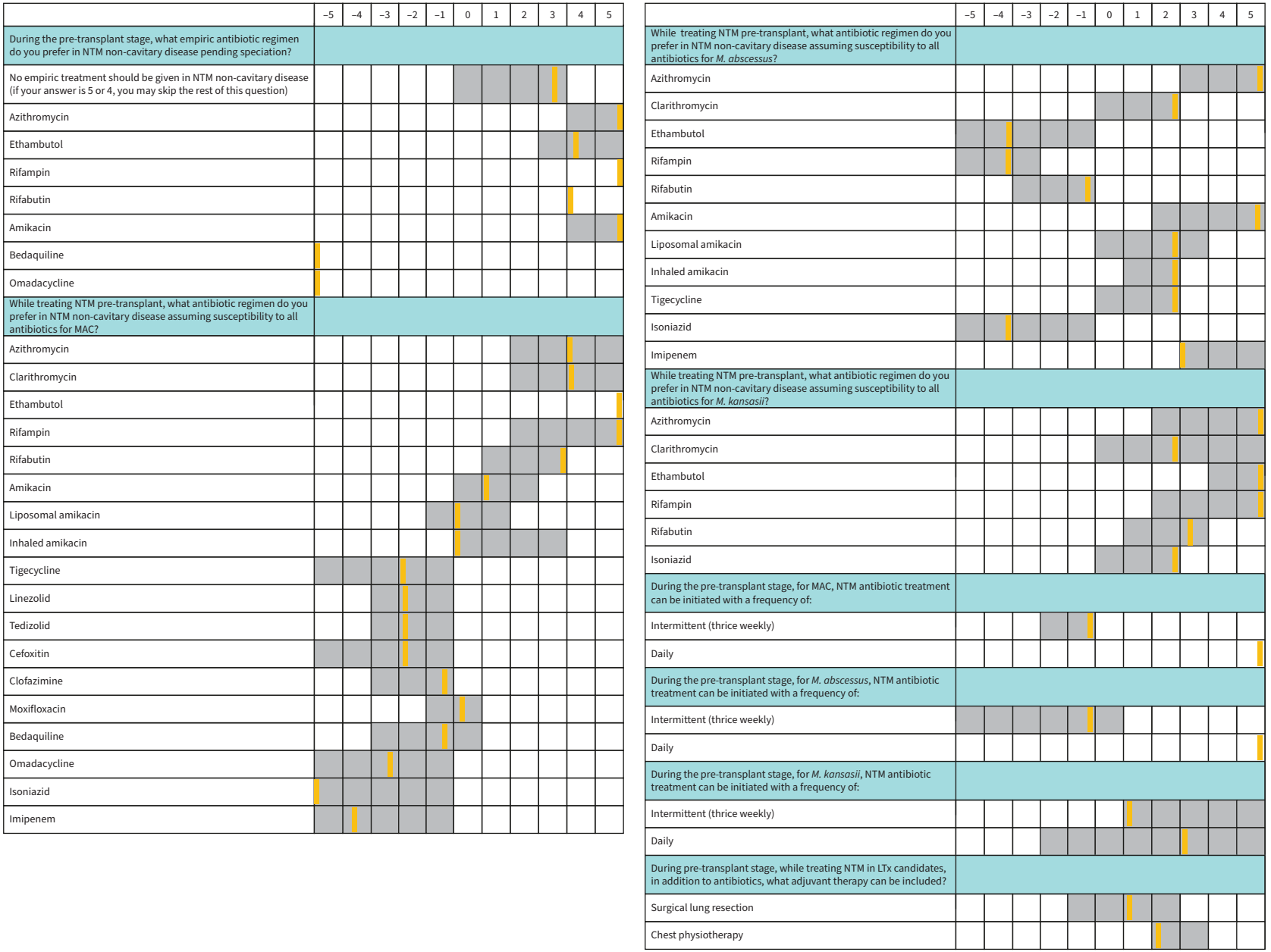

FIGURE 4 Summary of consensus on statements addressing pre-transplant management of nontuberculous mycobacteria (NTM) pulmonary disease. The grey and orange colours represent the range and median on a Likert scale of 11 points (5 to –5). A median rating >4 or < –4 indicates for or against the given statement, respectively. MAC: *Mycobacterium avium* complex; LTx: lung transplant.

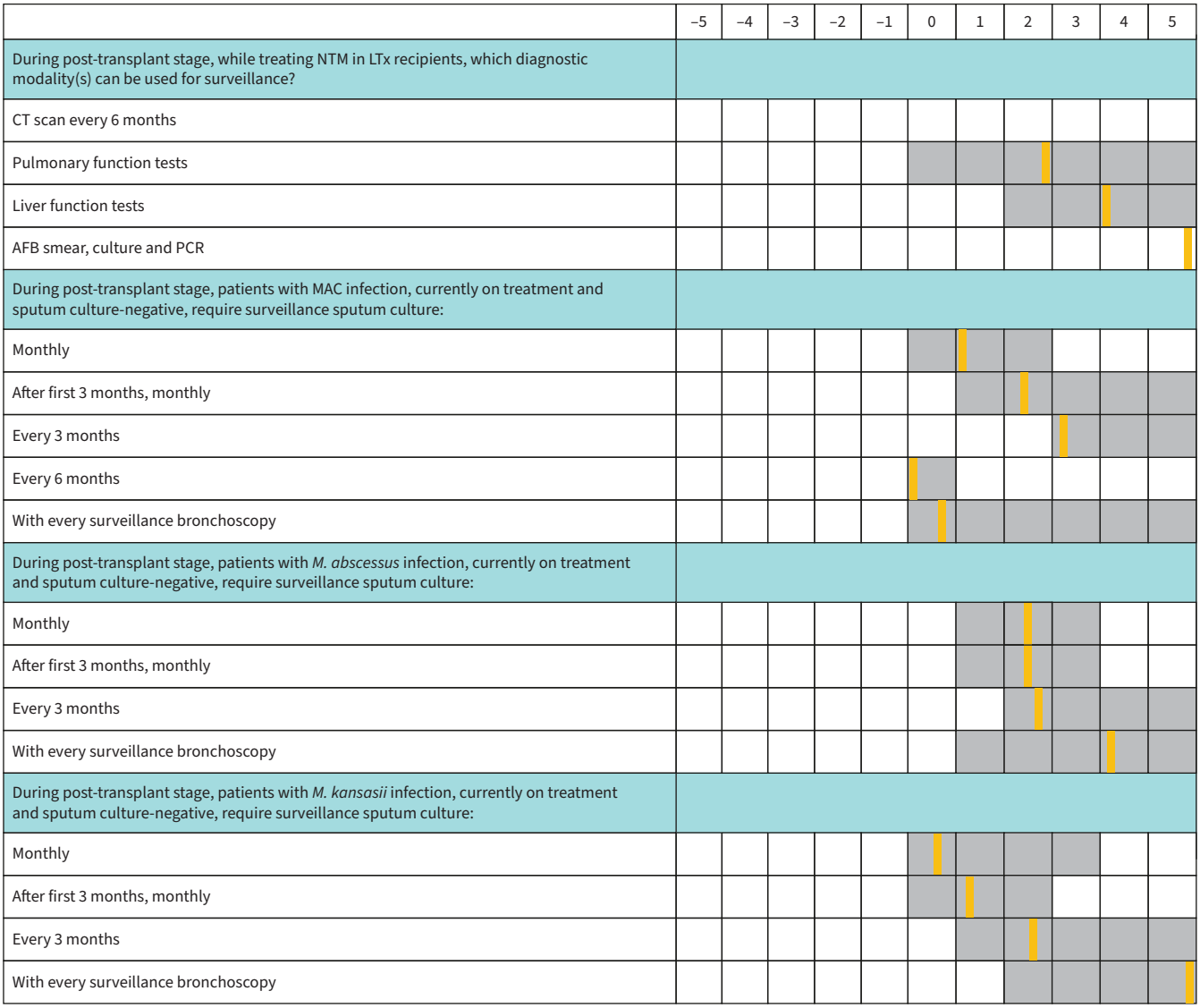

FIGURE 5 Summary of consensus on statements addressing post-transplant surveillance for nontuberculous mycobacteria (NTM) pulmonary disease. The grey and orange colours represent the range and median on a Likert scale of 11 points (5 to –5). A median rating >4 or < –4 indicates for or against the given statement, respectively. LTx: lung transplant; CT: computed tomography; AFB: acid-fast bacilli; MAC: *Mycobacterium avium* complex.

LTx listing criteria

During the pre-transplant stage, if the LTx candidate was on treatment for MAC infection and currently sputum culture-negative, it was agreed to list for LTx without further wait (4 (3–5)). For *M. abscessus*, the consensus was reached to list for LTx if sputum culture was negative for 12 months (4 (3.75–5)). The agreement was reached to list candidates with *M. kansasii* for LTx if sputum culture was negative for at least 6 months (4 (3–5)).

LTx candidates with a history of completed treatment for MAC infection who are currently sputum culture-negative should be listed for LTx if treatment was completed at least 12 months ago (4 (3–5)). In *M. abscessus* and *M. kansasii* infections, candidates should be listed for LTx if the treatment was completed 12 months (4.5 (3–5)) and 6 months (4 (3–5)) ago, respectively.

In candidates with a history of *M. abscessus* infection and current negative sputum cultures, the consensus was reached for bilateral (rather than single) LTx (4 (3–5)).

TABLE 1 Summary of key recommendations by experts

Diagnostic modalities for pre-transplant NTM pulmonary disease
Chest CT scan and sputum culture are suggested for NTM screening in LTx candidates.
Bronchial washing AFB smear and culture are suggested for NTM screening in donor lung before LTx.
Sputum/BAL fluid cultures should be sent to reference labs for NTM identification and susceptibility testing.
Transplant listing criteria in patients with NTM pulmonary disease
Experts have different opinions about patients with MAC infection who are currently on treatment and sputum culture-negative. Some suggest LTx without further waiting, others recommend culture negativity for the past 6 or 12 months. Experts did not agree that LTx is contraindicated irrespective of culture status.
Patients with *M. abscessus* infection who are currently on treatment and sputum culture-negative can be listed for lung transplant if the sputum culture has been negative for the past 12 months.
Patients with *M. kansasii* infection who are currently on treatment and sputum culture-negative can be listed for lung transplant if the sputum culture has been negative for the past 6–12 months.
Patients with a history of treated MAC and *M. abscessus* infection currently not on treatment and sputum culture-negative should be listed for lung transplant if treated 12 months ago, and 6 months ago in the patients with *M. kansasii*.
In patients with past history of *M. abscessus* infection and currently negative sputum culture who are candidates for single LTx, to prevent NTM infection in allograft perform bilateral LTx.
Pre-transplant management of NTM pulmonary disease
Azithromycin, rifampin, amikacin and rifabutin are suggested as empiric antibiotic regimen in NTM non-cavitary disease pending speciation.
The preferred antibiotic regimens in non-cavitary MAC include: ethambutol, rifampin, azithromycin and clarithromycin.
The preferred antibiotic regimens in non-cavitary *M. abscessus* include: azithromycin and amikacin.
The preferred antibiotic regimens in non-cavitary *M. kansasii* include: azithromycin, ethambutol and rifampin.
The recommended frequency of antibiotic therapy for MAC and *M. abscessus* is daily treatment.
Post-transplant surveillance for NTM pulmonary disease
AFB smear, culture, PCR and liver function tests can be used for surveillance while treating NTM in LTx recipients.
Patients with *M. abscessus* and *M. kansasii* infections currently on treatment and negative sputum culture require surveillance sputum cultures with every surveillance bronchoscopy.
Post-transplant management of NTM pulmonary disease
Clarithromycin and azithromycin are the most commonly preferred empiric antibiotic regimens (no identification yet) in non-cavitary disease. Some panellists suggest no empiric treatment.
The preferred antibiotic regimens in non-cavitary MAC include: ethambutol, rifampin, azithromycin and clarithromycin. In macrolide resistant patients, rifabutin and ethambutol are recommended.
The preferred antibiotic regimens in non-cavitary *M. abscessus* include: azithromycin, amikacin and imipenem.
The preferred antibiotic regimen in non-cavitary *M. kansasii* is rifabutin.
In the post-transplant stage, a dose reduction of immunosuppressive treatment is recommended if *M. abscessus* is isolated.

NTM: nontuberculous mycobacteria; CT: computed tomography; LTx: lung transplant; AFB: acid-fast bacilli; BAL: bronchoalveolar lavage; MAC: *Mycobacterium avium* complex.

Pre-transplant antibiotic treatment

Our study looked at individual antimicrobial recommendations in the pre-and post-transplant period. Combination regimens are beyond the scope of this study. The recommendations are for macrolide- and rifamycin-sensitive species unless otherwise specified.

In pre-transplant non-cavitary NTM disease pending identification, the consensus was reached for empiric use of macrolide (azithromycin (5 (4–5)), ethambutol (4.5 (3.25–5)), rifampin (5 (5–5)), rifabutin (4 (4–4)) and intravenous amikacin (5 (4–5)). 83.33% of panellists agreed to the same consensus for cavitary NTM disease pending identification.

MAC

Antibiotic treatment of non-cavitary MAC disease during the pre-transplant stage should include macrolides (azithromycin (5 (2.5–5)), clarithromycin (4.5 (2.5–5))) and ethambutol (5 (5–5)). Amongst the rifamycins, rifampin (5 (2.75–5)) reached consensus while rifabutin (3 (2–4)) did not. 66% of panellists recommended the use of the same antibiotic regimen for cavitary MAC disease as used in the non-cavitary condition, while 33% of panellists did not agree and recommended use of macrolides (azithromycin (4.5 (3.25–5)), clarithromycin (5 (3.5–5))), ethambutol (5 (5–5)) and rifamycins (rifabutin (4 (3–5)), rifampin (3 (3–3))) or intravenous amikacin (5 (4.25–5)).

M. abscessus

Pre-transplant antibiotic treatment of susceptible non-cavitary *M. abscessus* disease during the pre-transplant stage includes macrolides (azithromycin (5 (3.25–5)), clarithromycin (3 (0.75–3.5))), intravenous amikacin (5 (1.75–5)), liposomal inhaled amikacin (3 (0–4)), free inhaled amikacin (3 (1.5–3)), tigecycline (3 (0–3.25)) and imipenem (3 (2.75–5)). The use of the same regimen for cavitary disease was agreed upon by 75% of panellists.

M. kansasii

Pre-transplant treatment of susceptible non-cavitary *M. kansasii* disease includes macrolides (azithromycin (5 (2.25–5)), clarithromycin (3 (−0.25–5))), ethambutol (5 (4–5)) and rifamycins (rifampin (5 (2.5–5)), rifabutin (3.5 (1.75–2.5))). 91.6% of the panellists agreed with the same regimen for cavitary disease.

Post-transplant NTM surveillance

Post-transplant surveillance in LTx recipients receiving treatment for NTM infection should include an AFB smear, mycobacteria culture and PCR (5 (5–5)), liver function tests (5 (3–5)) and pulmonary function tests (4 (0–5)), in descending order of consensus rating.

In patients with post-transplant *M. abscessus* or *M. kansasii* infection currently on treatment and sputum culture-negative, the consensus was reached for surveillance sputum cultures with every surveillance bronchoscopy (4.5 (2.25–5) and 5 (2.25–5), respectively). No consensus was reached for MAC.

In post-transplant patients, NTM species isolated in two out of three sputum cultures or in one BAL culture should be considered clinically relevant if the isolated organism is *M. abscessus*, subspecies *M. abscessus* (5 (4–5)), *M. abscessus*, subspecies *M. massiliense* (5 (4–5)), *M. kansasii* (5 (3.75–5)), MAC, subspecies *M. avium* (4 (3.75–5)), MAC, subspecies *M. intracellulare* (4 (3.75–5)), MAC, subspecies *M. chimera* (4 (3–5)), *M. abscessus*, subspecies *M. bolletii* 4.5 ((3.75–5)) and *M. xenopi* (4 (2.5–5)).

Post-transplant antibiotic treatment

In post-transplant non-cavitary NTM disease pending identification, the consensus was reached not to use empiric antibiotic therapy (4 (3–5)). However, 33% of panellists rated empiric antibiotics, including macrolides (clarithromycin (4.5 (4–5)), azithromycin (4 (4–4))), ethambutol (4 (4–4.25)) and rifamycins (rifampin (4 (4–4.25), rifabutin (4 (4–4))). 83.33% of panellists recommended using the same regimen for cavitary disease as used in non-cavitary conditions.

In post-transplant NTM disease caused by MAC, *M. abscessus* or *M. kansasii*, the consensus was reached for daily antibiotic treatment (5 (4–5)).

MAC

Post-transplant antibiotic regimen in treatment-naive non-cavitary MAC disease include macrolides (azithromycin (5 (3.75–5)), clarithromycin (3 (−2.25–5))), ethambutol (5 (5–5)) and rifamycins (rifabutin, 3.5 (3–5)). Rifampin did not reach consensus (1.5 (−3–3)). 83.33% of panellists recommended using the same regimen for cavitary MAC disease.

In post-transplant MAC disease with macrolide resistance, the consensus was reached for the use of ethambutol (5 (4.75–5)), rifamycins (rifabutin (5 (3.75–5)), rifampin (3 (−3.25–3.25))) and free inhaled amikacin (3.5 (1–5)).

Post-transplant non-cavitary treatment-naive MAC infection should be treated for 12 months after sputum culture conversion (4 (3–4.25)).

M. abscessus

Post-transplant, the antibiotic regimen in treatment-naive non-cavitary *M. abscessus* disease should include macrolides (azithromycin (5 (3.75–5))), intravenous amikacin (5 (3.75–5)) and imipenem (5 (3.25–5)). No consensus was reached for liposomal inhaled amikacin (0 (0–4.25)), free inhaled amikacin (2 (0–4.25)) and clarithromycin (0.5 (−3–3.5)). 100% of panellists recommended using the same antibiotic regimen for cavitary *M. abscessus* disease.

In post-transplant *M. abscessus* disease with macrolide resistance, consent census was reached for the use of intravenous amikacin (4 (3.75–5)), free inhaled amikacin (4 (3–5)) and imipenem (5 (3–5)).

Post-transplant non-cavitary treatment-naive *M. abscessus* disease infection should also be treated for 12 months after sputum culture conversion (4 (3–4)).

M. kansasii

Post-transplant, the antibiotic regimen in treatment-naive non-cavitary *M. kansasii* disease should include ethambutol (5 (5–5)), rifamycins (rifabutin (4 (1.75–5))) and macrolides (azithromycin (3.5 (2.25–5))). No consensus was reached for rifampin (0 (−3.25–4)) or clarithromycin (0.5 (−3.5–3.25)). 100% of panellists recommended using the same regimen for cavitary disease.

In post-transplant *M. kansasii* disease with macrolide resistance, the consensus was reached for the use of ethambutol (5 (4–5)), rifamycins (rifabutin (4 (3.75–5)), rifampin (0.5 (3.75–5))) and isoniazid (4 (0.75–5)).

83.33% of panellists recommended the use of the same duration of antibiotic treatment for post-transplant cavitary treatment-naive *M. abscessus* disease as used in post-transplant non-cavitary *M. abscessus* disease. In comparison, 16.67% of panellists agreed to treat patients until 12 months after cavitary closure on chest CT scan (4 (4–4)).

Post-transplant non-cavitary treatment-naive *M. kansasii* disease infection should be treated for 12 months after sputum culture conversion (4 (3–4)).

Reduction in immunosuppression in post-transplant NTM infection

Post-transplant, a dose reduction of immunosuppression while treating NTM infection was agreed with consensus for *M. abscessus* (4 (3.75–5)). No agreement was reached regarding the reduction of immunosuppression for MAC infection.

While treating *M. abscessus* infection, a reduction in immunosuppression can best be achieved by reducing the dose of steroids (4 (3–5)). No consensus was reached for the dose reduction of mycophenolate mofetil (3 (3–4.25)) or tacrolimus (3 (3–4)).

Discussion

Our international panel of NTM and LTx experts completed three Delphi surveys to form consensus recommendations on managing NTM colonisation or infection in LTx candidates and recipients. Panellists agreed on numerous essential management strategies unique to the LTx population, including pre-transplant screening, timing and suitability of transplant, antibiotic therapy and immunosuppression. Our major recommendations are summarised in table 1.

Few data are available to guide NTM screening in LTx candidates. Our panellists recommended using sputum culture and chest CT. These modalities are also recommended for diagnosing general NTM pulmonary disease per American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) 2020 guidelines [26, 27]. Screening with sputum culture is usually followed by molecular identification of species [26].

There also needs to be more literature on NTM screening recommendations for the donor's lung. Some studies have used AFB smear and culture of bronchial washing or biopsies of donor's lung to screen for mycobacterial pulmonary disease [28, 29]. Our panellists recommend the routine use of bronchial washing AFB smear and culture [26]. According to ATS/IDSA 2020 guidelines on the management of NTM, identifying species is recommended for diagnosing all clinically relevant NTM species. In contrast, in the case of *M. abscessus*, identification of subspecies is recommended [26]. NTM pulmonary disease, especially with *M. abscessus*, is a contraindication to transplant in many centres as these species are notorious for the recurrence of disease [11]. However, there is little literature to support contraindications to transplants, which seems to be based on expert opinion.

While recent studies suggest an association of pre-transplant positive sputum culture with increased incidence of infection by *M. abscessus* in the post-transplant period, these studies noted successful treatment of the post-LTx *M. abscessus* infection and mortality from non-NTM causes [30, 31]. Another significant concern in these patients is the post-transplant drug interactions between immunosuppressants and antimicrobials. In our Delphi study, panellists recommend against absolute contraindication to LTx even with multiple positive sputum cultures for MAC, *M. abscessus* or *M. kansasii.* In a recent retrospective single-centre study that looked at outcomes of NTM pulmonary disease, the treatment success rate was noted to be highest in *M. kansasii* at 89.9%, followed by MAC at 65% and *M. abscessus* at 36.1%. A similar pattern was reported in culture concentration with *M. kansasii* at 4 months, MAC at

10 months and *M. abscessus* at 24 months [32]. Our experts, however, agreed that MAC patients on antimicrobial treatment and culture harmful could be listed for LTx without further delay. However, in the case of *M. kansasii* infection, 6 months of culture-negative while on treatment was recommended. A 12-month further treatment from culture-negative was recommended in *M. abscessus* before listing for LTx.

IDSA/ATS 2020 guidelines recommend species identification and susceptibility testing before starting treatment. However, as the peri- and post-transplant population tends to have altered immunity, our panellists lean towards empiric antibiotic therapy in pre- and post-transplant NTM disease. Our study looked at individual antimicrobial recommendations. Combination regimens are beyond the scope of this study. Offers are for macrolide- and rifamycin-sensitive species unless specified otherwise.

The treatment of MAC includes a three-drug regimen with a macrolide, ethambutol and a rifamycin. Macrolides are the critical component of antibiotic therapy, with an estimated 50–75% increase in the culture conversion [33]. While past studies have not demonstrated a consistent difference in efficacy, culture conversion rate or macrolide resistance, among the macrolides azithromycin is often preferred over clarithromycin due to its fewer drug interactions, lower pill burden and more irregular adverse effects [26, 34–36].

Using ethambutol, rifampin or clofazimine in the three-drug regimen has decreased macrolide resistance [26, 33, 37]. Our panellists recommend using macrolides, ethambutol and rifamycins in macrolide-sensitive MAC disease in pre-LTx candidates.

In the presence of severe nodular bronchiectatic or cavitary disease caused by MAC, the addition of a parenteral aminoglycoside, streptomycin or intravenous amikacin to the initial antibiotic regimen has been shown to improve culture conversion significantly and is recommended in the initial 2–4 months of treatment [26]. In our Delphi study, 66% of panellists recommended using the same antibiotics in cavitary MAC disease as a non-cavitary disease. In comparison, 33% recommended the use of intravenous amikacin in addition to the antibiotics mentioned above for cavitary infection.

In MAC pulmonary disease, a three-drug antibiotic regimen is recommended that contains ethambutol and rifampin in the presence of macrolide resistance. The third drug is often clofazimine, moxifloxacin or linezolid. Parenteral aminoglycosides including streptomycin or intravenous amikacin in the initial 2–3 months of treatment is also recommended by Kobashi *et al*. [38]. Including streptomycin for the initial 6 months of therapy, with adjunctive surgical resection, has also shown improved outcomes in macrolide resistance [39, 40]. Where sputum conversion is not achieved on antibiotic therapy for 6 months, the addition of liposomal inhaled amikacin is recommended, given its approved use in refractory MAC infection irrespective of macrolide resistance [26]. In our Delphi study, panellists recommend using free inhaled amikacin, ethambutol and rifampin. In our research, no consensus was reached on using clofazimine, moxifloxacin or linezolid in macrolide resistance.

Dosing frequency in the treatment of NTM is tailored to achieve improved outcomes while preventing macrolide resistance, reducing medication-associated adverse effects, and increasing medication compliance [26]. In non-cavitary MAC disease with macrolide susceptibility, IDSA/ATS guidelines recommend intermittent antibiotic therapy, while in cavitary conditions, daily dosing is recommended [26]. In *M. kansasii* non-cavitary and cavitary disease, thrice-weekly antibiotic dosing has been recommended while on a macrolide-based regimen. Daily dosing is recommended in isoniazid-based regimens. In our Delphi study, the panellists recommend daily antibiotic therapy for MAC, *M. abscessus* and *M. kansasii* infection. There is a paucity of literature on specific post-LTx treatment of NTM pulmonary disease. As these patients are immunosuppressed in the post-transplant period, our panel had a lower threshold to start antibiotic therapy and use daily dosing strategies with close monitoring for adverse drug reactions.

For post-transplant antibiotic therapy for all three species of NTM, our group was inclined to use the rifamycin rifabutin given its relatively less severe induction of hepatic enzymes and subsequently fewer drug interactions, particularly among patients receiving calcineurin inhibitors.

M. abscessus is the most common NTM responsible for post-LTx pulmonary NTM disease in the first 3 years following transplant [11]. The optimum treatment duration for *M. abscessus* is not set by guidelines. Current literature suggests a minimum duration of 12 months of treatment with an initial phase and a subsequent maintenance phase [26]. The treatment duration should be tailored considering the extent of disease with cavitary *versus* bronchiectasis/nodular findings, subspecies isolated, and susceptibility to macrolides and intravenous amikacin [26]. Our group recommended a longer duration for post-transplant treatment with antibiotics for 12 months after cavity closure on a CT scan. Patients with non-cavitary

disease can be treated until 12 months after sputum culture conversion. We also recommended decreasing immunosuppression for LTx recipients diagnosed with *M. abscessus* infection.

Our study had several limitations. While the Delphi process provided a systematic method for obtaining consensus, this method of consolidating expert opinions is not direct evidence-based. This project used a modified Delphi process, and there are only sometimes accepted criteria for agreement. Also, bias may have entered into the process by panel selection and during questionnaire development. This study's sample of panellists included 13 out of 18 (72%) USA-based participants. As a result, the findings may represent something other than a truly global perspective. Finally, panellists assessed individual antibiotics rather than antibiotic combinations used to treat NTM infections. Consensus antibiotic regimens may have differed from individual personal antibiotic choices.

Conclusion

This study provided expert opinion on the management of NTM in patients referred for LTx and recipients who develop post-transplant NTM infection. We addressed pre-transplant screening; timeline to transplant for candidates with NTM infection; and post-transplant management, including antibiotic selection and dosing frequency, duration of therapy and immunosuppression strategies. Until further evidence-based guidelines are available that address the unique profile of LTx candidates, these findings can be used as expert opinion.

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Conflict of interest: H. Asif, A. Ohsumi, J. Philley, A. Emtiazjoo, T. Hirama, C-C. Shu, F. Silveira, V. Poulin, M. Nagao, P-R. Burgel, S. Hays, T. Kawasaki, C. Dela Cruz, S. Aliberti, T. Nakajima, S. Ruoss, T.K. Marras and G.I. Snell have no conflict to report. F.F. Rahaghi has received research grants, paid to his institution, from Mallinckrodt, outside the submitted work; and payment or honoraria for lectures, presentations, consultation fee events from United Therapeutics, Mallinckrodt and Actelion Pharma, outside the submitted work. P. Rizzuto has received research grants, paid to his institution, from Insmed, regarding the submitted work. T. Aksamit has received payment or honoraria for lectures, presentations, consultation fee events from Advanced Respiratory, Inc., outside the submitted work. A.W. Baker has received research grants, paid to his institution, from NIH/NIAID, Insmed and CDC's Prevention Epicenters Program outside the submitted work. K. Winthrop has received restricted research grants, paid to his institution, from E.R Squibb & Sons, Regeneron Pharm and Gentech, outside the submitted work; and payment or honoraria for lectures, presentations, consultation fee events from Insmed, AbbVie, Eli Lilly and WhiteHall, outside the submitted work. M. Mirsaeidi has received research grants, paid to his institution, from Boehringer Ingelheim, Ashvattha and Mallinckrodt, outside the submitted work.

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