Epidemiology of Nontuberculous Mycobacterial Infections and Associated Chronic Macrolide Use among Persons with Cystic Fibrosis

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Rationale: Persons with cystic fibrosis (CF) are at high risk of nontuberculous mycobacterial (NTM) infection, with treatment requiring prolonged multidrug regimens that include macrolides. Although macrolides, specifically azithromycin, are used in the management of patients with CF with chronic *Pseudomonas*, macrolide-resistant NTM infections are of growing concern.

Objectives: To evaluate the relationship between chronic macrolide use and NTM infection among patients with CF included in the 2011 CF Patient Registry (CFPR).

Methods: We performed a nested case-control study: incident NTM cases were persons aged more than 5 years with at least one positive culture for NTM in 2011. Controls were persons with negative cultures in 2010 and 2011.

Measurements and Main Results: The 2011 CFPR included 27,112 patients; 5,403 (20%) were cultured for mycobacteria in 2010–2011 and met all inclusion criteria. Of these, 191 (4%) were NTM-positive in 2011 only (cases); 5,212 (96%) were NTM-negative in 2010 and 2011 (control subjects). Among the cases, 122 (64%) were culture-positive for *Mycobacterium avium* complex (MAC) and 69 (36%) for *M. abscessus*. Azithromycin use in 2010 was less frequently reported among MAC cases (57%; odds ratio = 0.7, $P < 0.05$) and *M. abscessus* cases (51%; odds ratio = 0.5, $P < 0.01$) than in control subjects (66%). Among adolescents and adults, patients with the greatest number of years on chronic macrolides were the least likely to develop incident NTM in 2011 ($P < 0.01$).

Conclusions: Patients with incident NTM infections from either MAC or *M. abscessus* were less likely to have had chronic azithromycin treatment in the past year. However, because macrolide monotherapy may lead to macrolide resistance, routine screening for NTM should be considered for persons with CF.

Keywords: macrolides; cystic fibrosis; nontuberculous mycobacteria

Persons with cystic fibrosis (CF) are at significantly greater risk of contracting nontuberculous mycobacterial (NTM) infections than the general population, with an estimated disease prevalence of 13–23% among all patients with CF (1, 2). Furthermore, recent research demonstrates that NTM is prevalent in

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Patients with cystic fibrosis (CF) are at increased risk for nontuberculous mycobacterial (NTM) infections. Treatment requires prolonged use of multidrug regimens that include a macrolide. However, macrolides are also increasingly used for the general management of CF because of their antiinflammatory properties, raising concerns over the potential development of macrolide-resistant NTM infections from long-term macrolide use. Clarifying the relationships between long-term macrolide therapy and NTM infections by species is vital for providing improved NTM treatment and prevention recommendations for the CF population.

What This Study Adds to the Field

We assessed chronic macrolide use and its association with NTM infections among persons with CF and found that incident NTM cases were significantly less likely to have had prior long-term azithromycin use.

CF populations globally (3–6), with *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* being the most commonly isolated species from patients with CF in the United States (1, 7). After an NTM infection is established in the airways of persons with CF, eradication is difficult and often requires prolonged use of multidrug treatment regimens that include a macrolide (8, 9), the only drugs for which *in vitro* susceptibility correlates with clinical outcomes and treatment response for NTM infections (8, 10). However, macrolides are also increasingly used for the general management of CF because of their antiinflammatory properties (11), raising concerns over the potential development of macrolide-resistant NTM infections from long-term macrolide use.

Macrolide-resistant pulmonary NTM infections in patients with CF are even more difficult to treat and have been associated with worsening pulmonary status (12), limiting patients' potential for future lung transplantation (13), and an increased risk of death (12). Furthermore, a recent study suggested a possible link between long-term macrolide use in patients with CF with an increased NTM infection rate, specifically theorizing that long-term azithromycin use may predispose patients with CF to infection with *M. abscessus* by facilitating mycobacterial survival through the blocking of intracellular autophagy, the immune response needed to clear these infections. This interference was thought to have led to chronic *M. abscessus* infections in a study of aerosol-infected mice after the acquisition of macrolide resistance by rapid induction of the *erm(41)* resistance gene (14).

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Macrolides play a critical role in the management and treatment of potentially life-threatening infections in patients with CF—an already vulnerable population. Therefore, clarifying the relationships among long-term macrolide therapy with NTM infections by species using nationally representative, population-level data is vital for providing improved NTM treatment and prevention recommendations for the CF population. The CF Patient Registry (CFPR) collects extensive data annually on more than 90% of all US patients with CF, including detailed mycobacterial data starting in 2010, facilitating the analyses needed to address this important question.

METHODS

To evaluate the effects of macrolide use on the development of incident NTM infections in patients with CF, we obtained CFPR data from 2003–2011 and performed a nested case-control study using individuals aged 5 years and older for whom a mycobacterial culture was performed in both 2010 and 2011 (collecting of specific data on performing mycobacterial cultures was initiated in 2010). Incident NTM cases included patients with a positive mycobacterial culture obtained in 2011 and a negative mycobacterial culture in 2010; patients with positive cultures obtained both years were excluded because they did not represent incident cases in 2011. Control subjects included all remaining patients with only negative mycobacterial cultures for both 2010 and 2011. Species-specific analyses evaluated MAC and *M. abscessus* cases only; patients culture-positive for other NTM species or multiple NTM species were excluded from these analyses. Additionally, CFPR data from 2003–2010 were used to further evaluate long-term macrolide use in incident NTM cases compared with control subjects. For this latter analysis, the case and control definitions were modified to include only individuals without NTM disease reported from 2003–2010. Patients were excluded from all analyses if they were transplanted in any year; were younger than 5 years of age at the end of 2011; died during the study period; were missing 2010 or 2011 data; or were positive for tuberculosis, NTM species other than MAC and *M. abscessus*, or multiple NTM species. This study was exempt from Institutional Review Board review at the National Institutes of Health.

Data Analysis

Incidence rates for NTM were calculated and baseline characteristics of cases and control subjects described using descriptive statistics. Significant differences between cases and control subjects were assessed ($P < 0.05$) for categorical variables using chi-square testing and univariate logistic regression. Significant variables in univariate models were considered for inclusion in multivariate regression models. Multivariate logistic regression models were used to identify any associations among presence and frequency of incident NTM infections and demographic, microbiologic, nutritional, genetic, clinical, and treatment-related variables. Patients placed on chronic macrolides, as determined by their physician, at any point during a given review year in the data registry were considered to have chronic macrolide exposure for that year. Classification of CF-transmembrane conductance regulator (CFTR) gene mutations that cause CF disease (15) was made using a previously published scheme (16, 17), which classifies CFTR mutations into five classes (I–V) according to their predicted effects on CFTR functioning (18); for this analysis, patients with class I, II, or III CFTR gene mutations were considered to have “severe CF genotypes” in comparison with those with class IV and V CFTR gene mutations. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to assess the ratio of exposure in cases compared with control subjects. Potential confounders were evaluated and included in models if they altered the estimated coefficients by greater than or equal to 10%. Effect modification of the association between macrolide therapy and incident NTM infection by age was considered and assessed by finding stratum-specific estimates in three age groups: (1) pediatric (5–12 yr old); (2) adolescent (13–17 yr old); and (3) adult (≥ 18 yr old). The pediatric lower limit was established at 5 years of age because of the inability of younger patients with CF to produce adequate sputum samples for mycobacterial cultures and to provide sufficient time to evaluate long-term macrolide exposure. All data were analyzed using SAS Version 9.3 (SAS Institute, Cary, NC).

RESULTS

Study Population

Of the 27,112 persons in the 2011 Cystic Fibrosis Foundation data registry, 6,571 (24%) received a mycobacterial culture in 2010 and 2011, and of these, 5,403 (20%) met all inclusion criteria. Of those meeting all inclusion criteria, 191 (4%) were NTM-positive in 2011 only (cases), whereas 5,212 (96%) were NTM-negative in both 2010 and 2011 (control subjects). Patients who had NTM reported before 2011 ($n = 819$), were infected with an NTM species other than MAC or *M. abscessus* in 2011 ($n = 52$), were infected with more than one NTM species ($n = 41$) in 2011, or who had *Mycobacterium tuberculosis* ($n = 3$) reported at any point were among those excluded (Figure 1).

Species-Specific Epidemiology

Of the 191 incident NTM cases, 122 (64%) had infections with MAC and 69 (36%) with *M. abscessus*. Incident MAC cases were similar to control subjects with respect to age (both averaged 25 yr); sex (48% vs. 51% male); and race (92% vs. 95% white). The mean body mass index for both MAC cases and control subjects was 46th percentile. MAC cases and control subjects also had similar FEV₁% predicted values (73% vs. 69%, respectively) and CF genotypes (94% vs. 96%, respectively, with severe CF genotype).

Incident *M. abscessus* cases were similar to control subjects with respect to age (both averaged 24 yr); sex (49% vs. 51% male); race (92% vs. 95% white); and body mass index percentile (40th vs. 46th, respectively). Proportion of severe CF genotypes was also similar among *M. abscessus* cases (96%) and control subjects (94%), although the FEV₁% predicted value was significantly higher in *M. abscessus* cases (76%) compared with control subjects (69%) (OR, 1.1 for each addition 5% FEV₁ increase; $P < 0.05$) (Table 1).

Concomitant Microbial Infections

MAC cases were significantly more likely than noncases to be concomitantly colonized with *Stenotrophomonas maltophilia* (OR, 1.6; $P < 0.05$) and *Aspergillus* sp. (OR, 1.7; $P < 0.001$), and significantly less likely to be colonized with *Pseudomonas aeruginosa* (OR, 0.7; $P < 0.05$). *M. abscessus* cases were significantly more likely than noncases to be colonized with *S. maltophilia* (OR, 2.9; $P < 0.001$) and *Aspergillus* sp. (OR, 3.1; $P < 0.001$) (Figure 2).

Macrolide Analysis

The association between macrolide exposure in 2010 and incident NTM infection in 2011 was characterized by species. Azithromycin was the most commonly used macrolide, accounting for 99% and 98% of all macrolide use for all NTM cases and control subjects, respectively. Among MAC cases, azithromycin use in 2010 was reported by 57%, whereas none reported clarithromycin use, compared with 66% and 1% of control subjects, respectively. In *M. abscessus* cases, azithromycin use was reported by 51% and clarithromycin by 1%. Both MAC and *M. abscessus* cases were significantly less likely than control subjects to report azithromycin use in 2010 (OR, 0.7, $P < 0.05$ and OR, 0.5, $P < 0.01$, respectively) (Table 2). Patients with CF who were colonized with *P. aeruginosa* in 2010 were over three times more likely to report azithromycin use in that same year (OR, 3.3; $P < 0.001$) and were also significantly less likely to be an incident NTM case in 2011 (OR, 0.6; $P < 0.01$).

Effect Modification by Age

The association between macrolide use and incident NTM cases varied by age (Table 2). The pediatric stratum comprised 834

Figure 1. Study population. CFF = Cystic Fibrosis Foundation; MABSC = *Mycobacterium abscessus*; MAC = *Mycobacterium avium* complex; NTM = nontuberculous mycobacteria.

persons (15% of all study patients), of whom 29 (4%) were incident NTM cases in 2011. Azithromycin use in 2010 was reported by 38% of pediatric cases compared with 44% of pediatric control subjects (OR, 0.8; 95% CI, 0.4–1.6). The adolescent stratum (those aged 13–17 yr) included 888 persons (16% of all study patients), of whom 47 (5%) were incident NTM cases. Among adolescents, cases were significantly less likely to report azithromycin use in 2010 compared with control subjects (43% vs. 50%; OR, 0.5; $P < 0.05$). Among the 3,681 (69%) adult study patients, 115 (3%) were incident NTM cases. Adult cases were also less likely to report azithromycin use in 2010 (64% vs. 73%; OR, 0.7; 95% CI, 0.5–1.0).

Long-Term Risk Factor Assessment

Past chronic macrolide use for greater than or equal to 1 year from 2003–2010 was reported by 64% of incident NTM cases

in 2011 (mean duration of use = 2.8 yr [range, 0–8 yr]) compared with 77% of control subjects (mean duration of use = 3.6 yr [range, 0–8 yr]). Both MAC and *M. abscessus* cases were significantly less likely to report past macrolide use compared with control subjects (OR, 0.5, $P < 0.001$ and OR, 0.6, $P < 0.05$, respectively). Among adolescents and adult patients with CF, those with greater numbers of years on chronic macrolides were even less likely to be an incident MAC or *M. abscessus* case in 2011. Furthermore, a significant dose–response effect ($P < 0.01$) was detected: patients with greater than or equal to 5 years on chronic macrolides were the least likely to be an incident MAC or *M. abscessus* case in 2011 (Table 3). Differences between long-term azithromycin and clarithromycin use could not be evaluated here because macrolide-specific data were incompletely reported from 2003–2009 in the CFPR.

TABLE 1. DEMOGRAPHIC AND CLINICAL FEATURES OF PATIENTS WITH CF AND WITHOUT INCIDENT NTM IN 2011, BY NTM SPECIES

Variable	MAC (n = 122)	MABSC (n = 69)	Control Subjects (n = 5,212)	Odds Ratio (95% Confidence Interval)	
				MAC	MABSC
Male, n (%)	58 (48)	34 (49)	2,642 (51)	0.9 (0.6–1.3)	0.9 (0.6–1.5)
White, n (%)	112 (92)	66 (96)	4,946 (95)	0.6 (0.3–1.2)	1.2 (0.4–3.8)
Severe genotypes, n (%) [†]	68 (96)	44 (96)	3,223 (94)	1.4 (0.4–4.3)	0.7 (0.2–2.8)
FEV ₁ , % predicted, mean ± SD*	73 ± 22	76 ± 24	69 ± 25	1 (0.99–1.1)	1.1 (1.0–1.1)
BMI%, mean ± SD*	46 ± 28	40 ± 25	46 ± 27	1.0 (0.95–1.0)	0.96 (0.9–1.0)
Age, yr, mean ± SD [‡]	25 ± 13	23 ± 13	25 ± 12	1.0 (0.99–1.0)	1.0 (0.96–1.0)
Age at CF diagnosis, yr, mean ± SD	5.2 ± 11	4.5 ± 9.4	4.1 ± 9.0	1.1 (0.98–1.2)	1.0 (0.9–1.2)

Definition of abbreviations: BMI = body mass index; CF = cystic fibrosis; MABSC = *Mycobacterium abscessus*; MAC = *Mycobacterium avium* complex; NTM = nontuberculous mycobacteria.

* Sample sizes with available data varied as follows: total population with genotyping, n = 3,534; total population reporting FEV₁, % predicted, n = 5,291; total population reporting BMI%, n = 3,095.

[†] Patients with CF with class I, II, or III CF-transmembrane conductance regulator gene mutations were considered to have “severe genotypes” in comparison with those with class IV and V CF-transmembrane conductance regulator gene mutations.

[‡] Age at the end of the 2011 review year.

Figure 2. Percentage of concomitant microbial infections and significant associations among patients with cystic fibrosis with and without incident nontuberculous mycobacteria infections, by species, 2011. Odds ratios displayed above significant associations. MABSC = *Mycobacterium abscessus*; MAC = *Mycobacterium avium* complex. * $P < 0.05$; ** $P < 0.01$.

DISCUSSION

Recently, major concerns have been raised within the CF community regarding a possible causal relationship between the increased use of long-term azithromycin for the management of CF and the concurrent increasing prevalence of *M. abscessus* infections in patients with CF (14, 19–21). Using a large cohort that includes more than 90% of the US population of patients with CF, we provide population-based evidence that patients with chronic azithromycin use are significantly less likely to develop incident NTM infections from either MAC or *M. abscessus* among adolescents and adults with CF. Additionally, we found that this relationship exhibited a dose–response effect, with greater numbers of years on chronic macrolides providing even more protection against developing NTM infections among patients without a prior NTM diagnosis.

Prior epidemiologic and experimental studies have provided conflicting findings regarding the relationship between azithromycin use and NTM in patients with CF, and possible mechanisms supporting an increased risk for NTM among azithromycin users. In a study comparing 30 *M. abscessus* case-patients with 60 negative control subjects, Catherinot and coworkers (21) found a protective, although not statistically significant, association between

M. abscessus lung disease and long-term low-dose azithromycin use. However, this study defined long-term azithromycin use as greater than or equal to 3 consecutive months at any point over a 4-year period before *M. abscessus* isolation in patients with CF, limiting the authors' ability to discern a strong causal association among past azithromycin use and infection with *M. abscessus*, because of the nonspecificity of exposure measurement (21). Another multicenter, cross-sectional study conducted in Israel showed that patients with CF with NTM were more frequently on treatment with azithromycin compared with control subjects (72% of cases compared with 51% of control subjects). However, this study captured azithromycin use concurrently with NTM assessment, so a temporal association between azithromycin and NTM infection could not be determined (5). Additionally, a recent murine study suggested a possible link between macrolide use and increased risk of NTM infection; however, whether this occurs in human populations remains to be investigated (14).

The true measure of the association between prior azithromycin use and incident *M. abscessus* infections may have been underestimated in our study, because *M. abscessus* is now thought to possibly be comprised of several subspecies (ss.), including *M. abscessus sensu stricto*, *M. abscessus* ss. *massiliense*, and *M. abscessus* ss. *bolletii* (22), which may respond differently

TABLE 2. NUMBERS AND PERCENTAGES OF PATIENTS WITH CYSTIC FIBROSIS WITH AND WITHOUT INCIDENT NONTUBERCULOUS MYCOBACTERIA INFECTION IN 2011 ON AZITHROMYCIN IN 2010, AND THE ASSOCIATED ODDS RATIOS BY AGE GROUP AND NONTUBERCULOUS MYCOBACTERIA SPECIES

Patient Population	Azithromycin Use in 2010, n (%)		OR	95% CI
	Cases	Control Subjects		
All patients (n = 5,403; n _c = 191)	105 (55)	3,443 (66)	0.6	0.5–0.8*
MAC (n = 122)	70 (57)	—	0.7	0.5–0.99†
MABSC (n = 69)	35 (51)	—	0.5	0.3–0.9†
Adults (n = 3,681; n _c = 115)	74 (64)	2,586 (73)	0.7	0.5–1.0
MAC (n = 79)	49 (62)	—	0.6	0.4–0.98†
MABSC (n = 36)	25 (69)	—	0.9	0.4–1.8
Adolescents (n = 888; n _c = 47)	20 (43)	499 (59)	0.5	0.3–0.9†
MAC (n = 30)	15 (50)	—	0.7	0.3–1.4
MABSC (n = 17)	5 (29)	—	0.3	0.1–0.8†
Pediatrics (n = 834; n _c = 29)	11 (38)	358 (44)	0.8	0.4–1.6
MAC (n = 13)	6 (46)	—	1.1	0.4–3.2
MABSC (n = 16)	5 (31)	—	0.6	0.2–1.6

Definition of abbreviations: Adolescents = 12–17 years old; Adults = greater than or equal to 18 years old; CI = confidence interval; MABSC = *Mycobacterium abscessus*; MAC = *Mycobacterium avium* complex; n_c = total incident nontuberculous mycobacteria case sample size; OR = odds ratio; Pediatrics = 5–11 years old.

* $P < 0.01$.

† $P < 0.05$.

TABLE 3. ASSOCIATION OF PAST CHRONIC MACROLIDE USE WITH INCIDENT NONTUBERCULOUS MYCOBACTERIA INFECTION AMONG ADOLESCENTS AND ADULTS (≥ 12 YR OLD) WITH CYSTIC FIBROSIS

Duration of use (yr)	2003–2010 Macrolide Use, n (%)				Odds Ratio (95% Confidence Interval)		
	MAC (n = 111)	MABSC (n = 55)	All Cases (n = 166)	Control Subjects (n = 4,523)	MAC	MABSC	All Cases
0	39 (35)	15 (27)	54 (33)	833 (18)	Reference	Reference	Reference
1–2	19 (17)	10 (18)	29 (17)	830 (18)	0.5 (0.3–0.9)*	0.7 (0.3–1.5)	0.5 (0.3–0.9) [†]
3–4	17 (15)	15 (27)	32 (19)	758 (17)	0.5 (0.3–0.9)*	1.1 (0.5–2.3)	0.7 (0.4–1.0)
5+	36 (32)	15 (27)	51 (31)	2,102 (46)	0.4 (0.2–0.6) [†]	0.4 (0.2–0.8) [†]	0.4 (0.3–0.6) [†]
Any macrolide use	72 (65)	40 (73)	112 (67)	3,690 (82)	0.4 (0.3–0.6) [†]	0.6 (0.3–1.1)	0.5 (0.3–0.7) [†]

Definition of abbreviations: MABSC = *Mycobacterium abscessus*; MAC = *Mycobacterium avium* complex.

* $P < 0.05$.

[†] $P < 0.01$.

to macrolide treatment. In one experimental study using a murine model, azithromycin and clarithromycin varied in their effectiveness against different subspecies of *M. abscessus* in the absence of underlying lung disease. Specifically, azithromycin had a greater antibiotic effect against *M. abscessus sensu stricto*, whereas clarithromycin was more effective against *M. abscessus* ss. *massiliense* (22). These results suggest that long-term azithromycin use in patients with CF may be even more effective in preventing NTM infections from certain subspecies relative to others. Although we were unable to distinguish among subspecies of *M. abscessus* in this analysis, this effect is important to consider for future studies comparing risks and benefits associated with different macrolide-based regimens. Additionally, we could not assess the effect of long-term clarithromycin here given the limited numbers of patients on this medication (only one case and one control subject in our final study population reported prior clarithromycin use).

This study has important diagnostic and therapeutic implications for patients with CF. Currently, the American Thoracic Society and Infectious Diseases Society of America recommend that adolescent and adult patients with CF be screened at least annually for NTM, and that patients of all ages be screened for NTM when experiencing periods of clinical decline while unresponsive to treatment for other possible pathogens (8). Patients on macrolide monotherapy (such as those being treated with pseudomonal infections) should be screened for NTM before starting therapy and regularly thereafter, because of concerns of acquisition of resistance (8). Although we found that the proportion of those cultured for NTM has increased since 2010, 76% of the cohort did not have a mycobacterial culture reported for 2010 and/or 2011. Because of the significant morbidity and mortality associated with NTM disease in patients with CF, routine screening and reporting of NTM is critical. American Thoracic Society and Infectious Diseases Society of America treatment guidelines also include species-specific recommendations. For MAC, the recommended treatment regimen includes a daily or three-times-weekly drug regimen with a macrolide in combination with ethambutol and a rifamycin until culture-negative for at least 1 year while on therapy (8). No antibiotic regimen of proved efficacy has been established for treatment of *M. abscessus* (8). Although our analysis evaluated the prevention of an initial NTM infection versus treatment of an active infection, our results suggest that azithromycin-based regimens may be effective for preventing *M. abscessus* infections. Differences behind the mechanisms of each macrolide in preventing and treating infection, and inducing resistance, remain unknown. Future investigations using population-level data are needed to better examine these relationships.

This study is subject to several important limitations. From 2003–2009, NTM disease status was incompletely reported in

the CFPR: positive results were not routinely reported and negative results were never reported. Therefore, it is impossible to know which patients received mycobacterial cultures before 2010, or to guarantee that those who were culture-positive were always reported. Thus, some of our cases and control subjects may have in fact been positive for NTM at some point in the past, but this information went unreported in the CFPR. Given the often chronic nature of NTM disease, this potential bias may have had a greater impact on those individuals identified as cases in 2011 than in the control group. However, this may mean that the protective association of azithromycin use for incident NTM infections is even greater (i.e., more protective) than that observed here. Another limitation is that our incident case definition included patients with one or more positive cultures for NTM in 2011. This definition was used because encounter-level data, which would reflect each mycobacterial culture performed and its result within the year, are not always completely reported; after a patient is identified as having NTM during a given year in the CFPR, the CF center may opt to not enter a second culture (based on current data entry requirements). Therefore, by including patients with only one positive NTM culture result in 2011 as incident cases, we may have included patients who were only transiently colonized with NTM but were perhaps not experiencing true NTM disease. However, this effect would result in our cases actually being more similar to control subjects and would therefore reduce any associations more toward the null. Thus, our findings here are likely even more significant in those meeting a more specific NTM case definition. Additionally, this analysis relied on annualized data for which dates of diagnosis, culture, and therapy time-points were not specified; however, our findings do show that the reporting of mycobacterial data and macrolide use over the past decade is increasing, and the associations between them have important implications for NTM treatment and prevention among patients with CF. Lastly, it is important to note that patients who received a mycobacterial culture may differ in their clinical presentation from those who did not; however, culture and/or routine screening practices vary widely, making it difficult to assess whether or not this affects the generalizability of our findings to patients who did not receive a mycobacterial culture.

In summary, long-term azithromycin use in persons with CF seems to be associated with a lower frequency of incident NTM infections. These results differ from previously published experimental data from *in vitro* models suggesting that prolonged azithromycin use confers increased risk for NTM infection, especially *M. abscessus*, in persons with CF (14). Additional research is still needed to understand why prior azithromycin use may be protective for preventing NTM infection, and to elucidate the biologic mechanisms behind this effect. Concerns of

macrolide resistance should be taken into account when long-term macrolide monotherapy is prescribed for the management of patients with CF. Routine screening for NTM in patients with CF should be considered, particularly for patients on macrolide monotherapy, because individuals on macrolide monotherapy who contract NTM are at greater risk for developing macrolide-resistant infections, which are associated with poor clinical outcomes, including severe morbidity and even death in patients with CF (12, 23).

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