Chronic Azithromycin Use in Cystic Fibrosis and Risk of Treatment-Emergent Respiratory Pathogens

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Abstract

Rationale: Azithromycin has been shown to improve lung function and reduce the number of pulmonary exacerbations in patients with cystic fibrosis. Concerns remain, however, regarding the potential emergence of treatment-related respiratory pathogens.

Objectives: To determine whether chronic azithromycin use (defined as three-times weekly administration) is associated with increased rates of detection of eight specific respiratory pathogens.

Methods: We performed a new-user, propensity score-matched retrospective cohort study utilizing data from the Cystic Fibrosis Foundation Patient Registry. Incident azithromycin users were propensity score matched 1:1 with contemporaneous nonusers. Kaplan-Meier curves and Cox proportional hazards regression were used to evaluate the association between chronic azithromycin use and incident respiratory pathogen detection. Analyses were performed separately for each pathogen, limited to patients among whom that pathogen had not been isolated in the 2 years before cohort entry.

Results: After propensity score matching, the mean age of the cohorts was approximately 12 years. Chronic azithromycin users had a significantly lower risk of detection of new methicillin-resistant *Staphylococcus aureus*, nontuberculous mycobacteria, and *Burkholderia cepacia* complex compared with nonusers. The risk of acquiring the remaining five pathogens was not significantly different between users and nonusers.

Conclusions: Using an innovative new-user, propensity score-matched study design to minimize indication and selection biases, we found in a predominantly pediatric cohort that chronic azithromycin users had a lower risk of acquiring several cystic fibrosis-related respiratory pathogens. These results may ease concerns that chronic azithromycin exposure increases the risk of acquiring new respiratory pathogens among pediatric patients with cystic fibrosis.

Keywords: cystic fibrosis; macrolides; microbiology; methicillin-resistant *Staphylococcus aureus*

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Azithromycin is a second-generation macrolide antibiotic used in cystic fibrosis (CF), chronic obstructive pulmonary disease, and non-CF bronchiectasis, principally for its immunomodulatory and antiinflammatory properties. Azithromycin

has been shown to reduce proinflammatory mediators in alveolar macrophages (1) and CF-airway epithelial cells *in vitro* (2). Azithromycin also inhibits *Pseudomonas aeruginosa* (*Pa*) bacterial growth, protein synthesis, and biofilm formation (3).

Furthermore, at subinhibitory concentrations, azithromycin can decrease the production of numerous bacterial virulence factors, particularly in *Pa* isolates (4–7). Several randomized controlled trials evaluating chronic azithromycin use (defined as

administration three times weekly) have illustrated that azithromycin can decrease the number of antibiotic courses, increase lung function, and decrease the number of pulmonary exacerbations in patients with CF, with beneficial effects most prominent for *Pa*-positive patients (8–11).

Largely on the basis of these studies, 2013 CF Foundation pulmonary guidelines of care recommend chronic azithromycin use for individuals aged at least 6 years with persistent *Pa* infection to improve lung function and reduce exacerbations (12). According to the 2015 annual Cystic Fibrosis Foundation Patient Registry (CFFPR) report, 66.6% of individuals who were *Pa* positive and at least 6 years of age were reported as chronic azithromycin users (compared with 41.2% in 2003) (13). However, concerns exist regarding the potential for treatment-emergent respiratory pathogen acquisition related to chronic azithromycin exposure.

Chronic azithromycin use has been associated with the emergence of macrolide-resistant *Staphylococcus aureus* in small, retrospective studies from the Netherlands and Denmark (14–16) and with *Aspergillus* colonization in France (17). Two small, retrospective studies from Israel and England found a positive association between azithromycin therapy and detection of nontuberculous mycobacteria (NTM) (18, 19), although a more recent, larger case-control study utilizing the CFFPR found that individuals with *Mycobacterium avium* complex or *Mycobacterium abscessus* were less likely to be reported as using chronic azithromycin compared with individuals without either NTM infection (20). Macrolide resistance has been found to be higher in *Pa* isolates (particularly of the Leeds epidemic strain) from azithromycin users than nonusers, likely due to mutations in ribosomal RNA (21).

As chronic azithromycin use in patients with CF becomes more widespread, it is increasingly important to understand any associations between azithromycin and acquisition of CF respiratory pathogens. We hypothesized that chronic azithromycin use among patients with CF increases the risk of acquisition of eight specific respiratory pathogens: NTM, methicillin-resistant *S. aureus* (MRSA), *Pseudomonas aeruginosa* (*Pa*), multidrug-resistant *P. aeruginosa* (MDR-*Pa*), *Stenotrophomonas maltophilia*, *Aspergillus* species, *Achromobacter xylosoxidans*, and *Burkholderia cepacia*

complex (BCC). A better understanding of the risk of treatment-emergent respiratory pathogens associated with chronic azithromycin use could inform health care providers and patients regarding the potential balances of risks and benefits of chronic azithromycin therapy. Some of the results of this study have been previously reported in the form of an abstract (22).

Methods

We conducted a new-user, propensity score-matched cohort study to evaluate the association between chronic azithromycin use and time to acquisition of the eight specific CF respiratory pathogens listed above. We utilized 2008–2014 data from the U.S. CFFPR, which contains encounter-based information on health outcomes, clinical care, and demographic data on approximately 85% of individuals diagnosed in the United States with CF (23).

Azithromycin use was ascertained from clinical encounters recorded in the CFFPR. New azithromycin use was defined as initiation of chronic azithromycin therapy (i.e., the first encounter at which three-times weekly azithromycin therapy was recorded) after 2 years during which chronic azithromycin use was not recorded. As the CFFPR does not contain information on start and stop dates or medication adherence, an individual recorded as initiating chronic azithromycin therapy was considered a chronic azithromycin user for the remainder of the study. Because we were interested in treatment-emergent pathogen acquisition (i.e., new detection of the pathogen), we assembled separate cohorts for each pathogen, composed of patients free of that pathogen during the 2 years before azithromycin initiation or selection as a matched nonuser.

Additional inclusion criteria for all eight cohorts included confirmed CF diagnosis and age of at least 6 and less than 36 years at time of azithromycin initiation or selection as a matched nonuser; the latter age cutoff was chosen to avoid the inclusion of older, healthier patients who might affect generalizability. The cohort assembled to evaluate risk of treatment-emergent NTM was limited to patients at least 12 years old, as NTM can be isolated only from sputum samples and younger children do not typically expectorate. Exclusion criteria included history of lung or solid organ

transplantation before azithromycin initiation or selection as a matched nonuser. For each of the study pathogens, respiratory pathogen detection was defined as the first positive respiratory culture recorded in the CFFPR after azithromycin initiation or selection as a matched nonuser. MDR-*Pa* was defined as *Pa* exhibiting resistance to at least two of the following three antibiotic classes: aminoglycosides, fluoroquinolones, or β -lactams.

To minimize confounding by indication, azithromycin users were matched to contemporaneous nonusers at the time of initiation of chronic azithromycin therapy by one-to-one propensity score (PS) matching (24) without replacement, using a greedy nearest neighbor strategy with a caliper of 0.01 of the PS-logit. The PS model included demographic, clinical, and treatment-related covariates assessed over a 12-month period before PS matching. Covariates were chosen *a priori*, based on clinical relevance. Covariates included in the PS matching are illustrated in Table 1 (and each additional pathogen-specific table). When two or more nonusers had the same PS match, one was chosen at random. Azithromycin users without matching nonusers were excluded from the study. Nonusers who started chronic azithromycin during the observation period were switched to the azithromycin user cohort at the time of azithromycin initiation and matched to a nonuser with a similar propensity score.

Covariates were summarized using descriptive statistics. For the full, unmatched cohort, continuous variables were compared between azithromycin users and nonusers, using a two-sample *t* test or Wilcoxon rank sum test, whereas categorical variables were compared by Pearson's χ^2 tests. For the pathogen-specific PS-matched cohorts, continuous variables were compared between users and nonusers by a paired *t* test, and categorical variables were compared by McNemar's test. Kaplan-Meier curves and Cox proportional hazards regression analysis were used to determine the association between azithromycin use and time to pathogen detection during the observation period for each new-user PS-matched cohort. An additional subcohort analysis was performed to compare the risk of MDR-*Pa* detection between azithromycin users and nonusers in a cohort of patients *Pa*-positive at baseline. The number of exacerbations requiring intravenous (IV) antibiotics after matching

Table 1. Baseline characteristics of original, full unmatched cohort: *N* = 7,329

Characteristic	Azithromycin New-Users (<i>N</i> = 3,080)	Azithromycin Nonusers (<i>N</i> = 4,249)
Demographic		
Entry age, mean (SD), yr	17.5 ± 10.8	17.3 ± 10.8
Sex, male	50.9%	53.7%
Race/ethnicity		
White	94.9%	93.6%
African American	4.0%	5.0%
Other	1.1%	1.4%
Insurance type		
Private	50.2%	53.1%
Medicaid	42.9%	40.5%
Medicare	2.2%	1.9%
Other	4.7%	4.5%
Clinical		
Pancreatic enzyme use	94.1%	87.3%
CF-related diabetes, yes	13.6%	9.6%
Body mass index percentile, mean (SD)	48.8 ± 25.5%	51.9 ± 26.6%
FEV ₁ % predicted,* mean (SD)	82.0 ± 21.4%	87.7 ± 20.8%
ΔF508 status		
Homozygous	51.8%	44.2%
Heterozygous	37.2%	40.1%
Other	11.0%	15.7%
Pulmonary exacerbations requiring IV antibiotics	≥2: 47.0%	≥2: 31.3%
Inhaled tobramycin, yes	55.6%	39.6%
Inhaled colistin, yes	5.8%	3.7%
Inhaled aztreonam, yes	0.9%	0.5%
Dornase alfa, yes	82.9%	73.3%
Pathogens at baseline		
MRSA	30.4%	27.1%
<i>Aspergillus</i> species	20.0%	14.8%
BCC	3.3%	2.8%
<i>Achromobacter xylosoxidans</i>	9.3%	6.9%
MDR- <i>Pa</i>	7.2%	4.3%
<i>Stenotrophomonas maltophilia</i>	21.6%	16.2%
NTM, ≥12 yr	6.4%	7.1%
<i>Pseudomonas aeruginosa</i>	48.2%	31.6%

Definition of abbreviations: BCC = *Burkholderia cepacia* complex; CF = cystic fibrosis; FEV₁ = forced expiratory volume in 1 second; IV = intravenous; MDR-*Pa* = multidrug-resistant *Pseudomonas aeruginosa*; MRSA = methicillin-resistant *Staphylococcus aureus*; NTM = nontuberculous mycobacteria; SD = standard deviation.

*See Reference 24.

was compared between azithromycin users and nonusers to determine whether IV antibiotic exposure was different between the two groups. Analyses were performed with Stata 14.1 (StataCorp). This study was approved by the Institutional Review Board at Seattle Children's Hospital (Seattle, WA) and the CF Foundation Patient Registry Committee.

Results

Of the 26,914 children and adults monitored in the CFFPR in 2008, 7,329 met eligibility criteria and were available for cohort-specific PS matching (Figure 1). Baseline

characteristics of the full, unmatched cohort are described in Table 1. New azithromycin users ("new users") made up 42.0% of the unmatched cohort. In comparison with azithromycin nonusers, individuals who initiated azithromycin were more often pancreatic insufficient (94.1 vs. 87.3%; *P* < 0.001), had lower body mass index percentiles (mean ± SD: 48.8 ± 25.5 vs. 51.9 ± 26.6%; *P* < 0.001), and had lower baseline FEV₁ % predicted (82.0 ± 21.4 vs. 87.7 ± 20.8%; *P* < 0.001) (using Global Lung Function Initiative [GLI] reference equations [25]). In addition, azithromycin users were more often prescribed inhaled antibiotics within the 12-month period before matching,

including inhaled tobramycin (55.6 vs. 39.6%; *P* < 0.001), inhaled colistin (5.8 vs. 3.7%; *P* < 0.001), and inhaled aztreonam (0.9 vs. 0.5%; *P* = 0.032). Table E1 (in the online supplement) compares the characteristics of the excluded azithromycin prevalent users (*N* = 7,814) with the cohort eligible for matched analysis described in Table 1.

Table 2 describes the baseline characteristics of the PS-matched cohort assembled for evaluation of risk of acquisition of MRSA; no significant differences were seen between azithromycin users and nonusers for any of the variables included in the PS model, indicating that our PS matching was successful in minimizing differences between users and nonusers in the measured study variables. The entry age for the matched MRSA cohort was 12.1 ± 3.9 years in each group. The baseline characteristics of the matched cohorts for the seven additional study pathogens and subcohort analysis are presented in Tables E2–E9. Similar to the matched MRSA cohort, no significant differences between users and nonusers were seen for any covariates in any of the other cohorts.

The forest plot in Figure 2 illustrates the risk of detection of each of the eight respiratory pathogens by matched-pair analysis, using Cox proportional hazards survival analysis. For each cohort, at least 400 matched pairs were available for analysis. Compared with azithromycin nonusers, azithromycin users had a significantly lower risk of detection of new NTM (hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.41–0.87; *P* = 0.017), MRSA (HR, 0.65; 95% CI, 0.52–0.78; *P* < 0.001), and BCC (HR, 0.66; 95% CI, 0.42–0.90; *P* = 0.024). Although not statistically significant, a trend was seen toward higher risks of new MDR-*Pa* detection among azithromycin users compared with nonusers (HR, 1.31; 95% CI, 0.90–1.71; *P* = 0.092). A similar trend was seen in a subcohort analysis evaluating risk of new MDR-*Pa* in a *Pa*-positive only cohort. There were no differences between azithromycin users and nonusers in risk of acquisition of the remaining study pathogens. A Kaplan-Meier survival curve for the MRSA cohort is illustrated in Figure 3, and Kaplan-Meier curves for the remaining seven study cohorts (and one subgroup cohort) are shown in Figures E1–E8.

Figure 1. Study participant selection. *For each pathogen listed above, exclusion criteria included respiratory culture positivity for that pathogen during the baseline period or inability to be included in cohort due to poor propensity-score matching. CF = cystic fibrosis.

Table E10 describes the number and rate of pulmonary exacerbations requiring IV antibiotics among azithromycin users and nonusers for each pathogen cohort

during the observation period. Azithromycin users had significantly higher exacerbation rates than nonusers in the *Aspergillus* (incidence rate ratio [IRR], 1.07; $P = 0.002$),

MDR-*Pa* (IRR, 1.06; $P < 0.001$), and *Achromobacter xylosoxidans* (IRR, 1.06; $P < 0.001$) matched cohorts.

Discussion

Using CF Foundation Patient Registry data, we found, contrary to our hypothesis and to those of a number of prior small, single-center studies, that azithromycin users had lower risks of new acquisition of NTM, MRSA, and *Burkholderia cepacia* complex, compared with nonusers. Although these results are reassuring, any retrospective cohort study must be interpreted with caution because of potential residual confounding from unmeasured covariates that may explain the observed associations. We attempted to minimize these sources of error by using an innovative new-user, propensity score-matched cohort design. Indication bias arises in observational studies because treatment is not prescribed at random but rather is related to disease severity and other characteristics that affect risk of a future health outcome (26). Thus, disease severity must be accounted for in any modeling. For example, in our cohort, as we anticipated, azithromycin users were clearly on average sicker than nonusers (Table 1). Because of the large size and extensive clinical data contained in the CFFPR, we were able to utilize propensity score matching to minimize confounding by indication.

In tandem with propensity score matching, we restricted our analysis to new azithromycin users. This new-user design allowed for matching users and nonusers at the initiation of chronic azithromycin therapy, because chronic azithromycin therapy itself is likely to affect the characteristics on which participants are matched. In addition, a new-user design eliminates any chronology bias (arising from the fact that a treatment may affect outcomes differently depending on how long a patient has been using it) because the start of the study period is identical for azithromycin users and nonusers (27). The new-user, propensity score design essentially attempts to mimic a randomized controlled trial within a retrospective cohort study, matching patients via a propensity score at the time that chronic azithromycin therapy is initiated and monitoring them forward to observe for the outcome of interest (28). Although PS matching

Table 2. Baseline characteristics of matched methicillin-resistant *Staphylococcus aureus* cohort: N = 1,576

Characteristic	Azithromycin New-Users (N = 788)	Azithromycin Nonusers (N = 788)	P Value
Demographic			
Entry age, mean (SD), yr	12.1 ± 3.9	12.1 ± 3.9	0.99
Sex, male	52.3%	53.6%	0.61
Race/ethnicity			0.64
White	96.8%	95.9%	
African American	2.9%	3.6%	
Other	0.3%	0.5%	
Insurance type			0.59
Private	54.8%	52.5%	
Medicaid	42.9%	45.4%	
Other	2.3%	2.1%	
Clinical			
Pancreatic enzyme use	95.9%	95.3%	0.54
CF-related diabetes (yes)	5.5%	5.5%	0.80
Body mass index percentile, mean (SD)	49.9 ± 25.2%	50.4 ± 26.2%	0.70
FEV ₁ % predicted,* mean (SD)	91.6 ± 16.6%	91.4 ± 17.0%	0.78
ΔF508 status			0.72
Homozygous	53.3%	51.7%	
Heterozygous	35.5%	36.0%	
Other	11.2%		
Pulmonary exacerbations requiring IV antibiotics	≥2: 34.4%	≥2: 36.9%	0.29
Inhaled tobramycin, yes	45.4%	47.0%	0.54
Inhaled colistin, yes	2.8%	2.3%	0.52
Inhaled aztreonam, yes	0.1%	0.3%	0.56
Dornase alfa, yes	82.1%	83.2%	0.55
Pathogens at baseline			
MRSA	—	—	—
Aspergillus species	16.5%	15.0%	0.41
BCC	1.9%	1.5%	0.56
Achromobacter xylosoxidans	6.6%	7.4%	0.55
MDR-Pa	2.2%	1.9%	0.72
Stenotrophomonas maltophilia	23.5%	20.9%	0.23
NTM, ≥12 yr	3.8%	2.9%	0.52
Pseudomonas aeruginosa	36.4%	32.0%	0.06

Definition of abbreviations: BCC = *Burkholderia cepacia* complex; CF = cystic fibrosis; FEV₁ = forced expiratory volume in 1 second; IV = intravenous; MDR-Pa = multidrug-resistant *Pseudomonas aeruginosa*; MRSA = methicillin-resistant *Staphylococcus aureus*; NTM = nontuberculous mycobacteria; SD = standard deviation.

*See Reference 24.

reduced the overall sample size, after matching each pathogen-specific cohort had at least about 400 matched pairs, providing greater power than most prior studies to evaluate the risk of treatment-emergent pathogens.

In our cohort, azithromycin users had a lower risk of new NTM detection than nonusers. Our findings are in contrast to previous single-center studies from Israel (18) and England (19), but are similar to two nested case-control studies evaluating risk factors for NTM acquisition (20, 29). One of these was a small single-center study of adults from France that compared NTM case subjects (defined as at least one positive NTM respiratory culture) with control

subjects, and noted that azithromycin was associated with a twofold reduction in NTM isolation (29). The other case-control study utilized the U.S. CFFPR to examine the rate of chronic azithromycin use in the prior year among patients with first isolation of NTM from a respiratory culture and matched control subjects. The authors found that patients with incident NTM were less likely to have reported chronic azithromycin use in the past year (20). The Israeli, English, and French single-center studies were limited by relatively small sample sizes that reduce power and may affect generalizability. The larger CFFPR study was susceptible to indication bias, and so it is reassuring that our propensity score-

matched study also found a reduction rather than increased risk of NTM infection in those treated with chronic azithromycin.

Azithromycin has been shown to exhibit *in vitro* activity against *Mycobacterium avium* complex clinical isolates (30), and it is one of a relatively few oral antimycobacterial agents with an effect on some subspecies of *M. abscessus* (31–33). These findings illustrate that azithromycin has potential anti-NTM activity, providing a plausible explanation for the lower observed NTM detection rate in azithromycin users. However, azithromycin monotherapy can induce macrolide resistance in some NTM species (31), and for this reason, the 2016 CF Foundation and European Cystic Fibrosis Society NTM clinical care guidelines recommend the discontinuation of chronic azithromycin therapy among patients who are respiratory culture-positive for NTM (34). Unfortunately, the CFFPR does not capture NTM macrolide resistance. It is plausible that although azithromycin lowered the rate of NTM detection, it may have increased the proportion of macrolide-resistant NTM isolates, which might have therapeutic implications when initiating future NTM antibiotic therapy. Further research is needed to determine whether azithromycin use increases the risk of macrolide resistance in NTM (and particularly *M. abscessus*) infections.

Similar to NTM, MRSA infection in CF airways has been associated with lung function decline (35–37) and increased mortality (38). Our study found a decreased risk of new MRSA detection in azithromycin users compared with nonusers. Azithromycin use was previously associated with a reduction in *S. aureus* incidence in an epidemiological study from Denmark (16), although the incidence of macrolide-resistant *S. aureus* strains increased from 7% before azithromycin use to 52.5% after azithromycin initiation. Azithromycin use was associated with a decreased risk of methicillin-sensitive *S. aureus* in the 2003 randomized, controlled trial evaluating azithromycin in *Pa*-positive patients (9), but the 2010 follow-up trial in *Pa*-negative patients found an increased risk of new MRSA among participants randomized to azithromycin (11). Azithromycin has antimicrobial activity at subinhibitory concentrations (4–7) and has been shown *in vitro* to reduce the production of α -hemolysin and biofilm formation in

Figure 2. Forest plot illustrating hazard ratios associated with chronic azithromycin use for the eight respiratory pathogens. CI = confidence interval; HR = hazard ratio; MDR-*Pa* = multidrug-resistant *Pseudomonas aeruginosa*; MRSA = methicillin-resistant *Staphylococcus aureus*; NTM = nontuberculous mycobacteria.

MRSA (39). Although national antibiograms are not easily available, antibiogram data from our institution note 45% macrolide susceptibility among MRSA isolates (40). If this high level of macrolide susceptibility among MRSA isolates holds true in much of the United States, it could potentially account for the observed reduced MRSA detection in azithromycin users.

Hospitalization frequency and antibiotic exposure are known risk factors for MRSA acquisition in CF (36, 41). The

rate of pulmonary exacerbations requiring IV antibiotics during the observation period was not significantly different between azithromycin users and nonusers in the MRSA cohort. However, it is plausible that azithromycin users had fewer exacerbations treated with oral antibiotics compared with nonusers, resulting in a lower MRSA acquisition risk because increased antibiotic exposure has been associated with MRSA isolation (42). The two landmark randomized controlled trials evaluating

azithromycin use in *Pa*-positive (9) and *Pa*-negative patients (11) included pulmonary exacerbations treated with oral as well as IV antibiotics. In both studies, a statistically significant reduction was seen in the number of oral antibiotic courses among azithromycin users compared with those randomized to placebo. Interestingly, when IV antibiotic use was examined alone, *Pa*-positive azithromycin users tended to have fewer IV antibiotic courses compared with placebo (although not statistically significantly different), and *Pa*-negative azithromycin users had no significant difference in IV antibiotic use compared with placebo (9, 11). Unfortunately, a limitation of the CFFPR (at the time our data were collected) is the absence of reliable data on outpatient oral antibiotic use for the treatment of pulmonary exacerbations, and thus we were unable to accurately determine whether outpatient exacerbations occurred or whether oral antibiotics were administered more frequently in azithromycin users versus nonusers in our analysis.

The risk of new BCC detection was lower in azithromycin users compared with nonusers in our study. BCC is made up of at least 20 different bacterial species, of which three in particular (*B. multivorans*, *B. cenocepacia*, and *B. dolosa*) are considered most pathogenic in CF (43), and were isolated in our study in 25.3, 8.4, and 0% of BCC-positive respiratory cultures, respectively. Colonization with *B. cenocepacia* is considered a poor prognostic indicator in CF and has been associated with reduced lung function and survival (44, 45). To our knowledge, no previous studies have examined the association between azithromycin and acquisition of any member of the BCC. Both of the two aforementioned randomized trials evaluating azithromycin use in *Pa*-positive and *Pa*-negative patients (9, 11) found only one BCC-positive respiratory culture in an azithromycin-treated individual (compared with none in the placebo group). More research is needed into the reasons for the potentially decreased risk of BCC detection in azithromycin-treated patients.

This study has several important limitations. The most important is the potential for residual indication bias inherent in any retrospective cohort study. We attempted to minimize this bias with the use of propensity score matching, but residual indication bias (due to unmeasured

Figure 3. Kaplan-Meier plot of cumulative proportion of individuals methicillin-resistant *Staphylococcus aureus* (MRSA)-free by incident azithromycin exposure in the MRSA cohort. AZM = azithromycin.

confounders) might have affected the results. Misclassification of azithromycin use, respiratory culture results, or other covariates is an inherent limitation of this registry-based study (22). Because the CFFPR does not capture medication start and stop dates or medication adherence, we chose the most conservative approach to classifying azithromycin use. Similar to intent-to-treat analysis, once an individual started chronic azithromycin, he or she remained in the azithromycin-exposed group for the remainder of the observation period. We believed that any misclassification related to this approach would likely bias our results toward the null. Our new-user design and PS matching also created a predominantly pediatric cohort (mean age of 12 yr for all cohorts except NTM), which limits the generalizability of our results beyond the pediatric age range. We had a maximum of 5 years of observation, so we are unable to comment on longer-term risk of emergence of pathogens related to azithromycin use.

One of the greatest concerns regarding chronic azithromycin exposure

is the risk of inducing macrolide resistance (11, 21). Unfortunately, because the CFFPR does not contain information on macrolide resistance, we were unable to evaluate the risk of emergence of macrolide-resistant organisms in our cohort. Ultimately, our observation that azithromycin use was associated with a lower risk of acquisition of several CF pathogens could be mitigated if indeed the risk of macrolide resistance is increased. We were able to determine IV antibiotic use, but we could not reliably capture acute inhaled or oral antibiotic use for outpatient pulmonary exacerbation treatment from the CFFPR, limiting our ability to compare oral antibiotic use during follow-up between azithromycin users and nonusers as a potential explanation for differing risk of treatment-emergent organisms.

In conclusion, using a new-user, PS-matched cohort design with data from the U.S. CFFPR, we found in a predominantly pediatric cohort that azithromycin users had lower risks of detection of new MRSA, NTM, and BCC

compared with nonusers. The use of existing data for research in orphan diseases (like CF) avoids the huge expense and time required for clinical trials, allows for longer-term follow-up, and reflects “real world” clinical care. Therefore, retrospective registry-based studies utilizing innovative and rigorous methodological designs can play a valuable role in answering longitudinal questions in a feasible, timely, and cost-effective manner to improve the care of children and adults with CF. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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