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Azithromycin and Tobramycin Therapy in Cystic Fibrosis Pulmonary Exacerbations: Less Is More?

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Pseudomonas aeruginosa (*Pa*) is a principal pathogen in the lower airways of individuals with cystic fibrosis (CF), and chronic infection is associated with negative clinical outcomes, including decreased lung function (percentage predicted forced expiratory volume in 1 second [ppFEV$_1$]), risk of pulmonary exacerbations (PEx), and reduced survival (1–4). For decades, tobramycin has been used in the treatment of *Pa* for eradication, chronic suppression, and treatment of acute PEx. Chronic azithromycin (AZM) therapy, though not directly antipseudomonal, has become increasingly used (estimated 64% of persons aged 6 years and older) over the last decade, aiming to reduce the frequency of PEx in patients with CF bronchiectasis with or without chronic *Pa* infection (5, 6). Patients are often treated with multiple antipseudomonal therapies, including AZM and tobramycin, in combination to optimize clinical outcomes in both the acute and chronic settings. As medications tend to be additive over time in a person's disease course, the potentially antagonistic drug interactions are often overlooked. Encouragingly, recent studies have endeavored to evaluate just this and have identified antagonistic *in vivo* (7) and *in vitro* (8) interactions between commonly concurrently prescribed AZM and tobramycin in *Pa* infection.

In this issue of *AnnalsATS*, Cogen and colleagues (pp. 266–272) report the first and largest study addressing the relationship between concomitant chronic AZM and parenteral tobramycin use during acute PEx in patients with CF on clinical outcomes (9). They conducted a retrospective cohort study using the CF Foundation Patient Registry–Pediatric Health Information System (10) linked dataset and analyzed 2,294 children and adolescents with CF aged 6–21 years with 5,022 PEx across 45 U.S. hospitals between 2006 and 2016. An

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exacerbation was eligible with a minimum drop in ppFEV$_1$ of ⩾5% from baseline on admission. The primary outcomes were the change (pre–PEx treatment to post–PEx treatment) in ppFEV$_1$, the proportion recovering to ⩾90% of baseline ppFEV$_1$, and time to next PEx requiring intravenous antibiotics compared between patient groups. To further examine granularity around AZM exposure, the following three subgroups were identified with varying AZM use: those with AZM use during both PEx and at the most recent outpatient clinical encounter (group 1; 2,247 PEx), those who had AZM during outpatient encounter only (group 2; 477 PEx), and those with no recent exposure (group 3; 2,298 PEx). The AZM-exposed groups (1 and 2) were older, had a lower median ppFEV$_1$, and had a greater proportion of patients with chronic *Pa* infection. Group 1 patients had a significantly lower improvement in pre– to post–PEx treatment ppFEV1 (−0.93%; confidence interval [CI], −1.78 to −0.07; $P = 0.033$), lesser odds of returning to ⩾90% baseline ppFEV1 (odds ratio, 0.79; CI, 0.68–0.93; $P = 0.003$), and shorter time to next PEx requiring intravenous antimicrobial therapy (hazard ratio, 1.22; CI 1.14–1.31; $P < 0.001$) when compared with group 3. A similar trend was noted in group 2 compared with group 3, and although it did not reach statistical significance, it was underpowered because of the sample size of this group. An additional analysis was undertaken for intravenous colistimethate with and without AZM to address whether the antagonistic effect of two antimicrobials was class independent, and no significant differences were observed in any outcomes. Overall, the authors concluded that concomitant AZM and intravenous tobramycin use for in-hospital PEx treatment was associated with significantly lesser pulmonary improvements when compared with intravenous tobramycin alone.

This study is poignant because it reports on medications used in the acute setting and builds on observations around antagonism already reported in the literature. Nichols and colleagues used a retrospective *post hoc* analysis of a CF clinical trial for which subjects received 4 weeks of inhaled tobramycin immediately preceding 4 weeks of inhaled aztreonam (7). Among patients who were receiving concurrent AZM therapy, lesser benefit was observed in ppFEV$_1$ increase during the inhaled tobramycin period compared with inhaled aztreonam (mean FEV$_1$ change of 0.8% vs. 6.4%; $P < 0.005$). Notably, subjects not using AZM had no significant differences in mean FEV$_1$ change during these 4-week periods (mean FEV$_1$ of 2.6% vs. 3.6%; $P =$ not significant). Similarly, another retrospective cohort study assessing chronic AZM use with intravenous antibiotic regimens during PEx demonstrated poorer lung function recovery in patients receiving AZM with IV tobramycin (−3% relative ppFEV$_1$ recovery [95% CI, −0.7 to 0.2] and −2.644% absolute ppFEV$_1$ change [95% CI, −4.52 to −0.76]), whereas this was not the case when patients were treated with intravenous colistimethate (+3% relative ppFEV$_1$ recovery [95% CI, −0.1 to 7] and 2.00% absolute improvement in ppFEV$_1$ [95% CI, 0.13–3.87]) (11). In contrast, a subgroup analysis of the recently completed OPTIMIZE (Optimizing Treatment for Early *Pseudomonas aeruginosa* Infection in Cystic Fibrosis) trial identified that in pediatric patients with CF who were chronically prescribed tobramycin inhalation solution (TIS) for *Pa*-positive culture, there was no significant difference in eradication rates or clinical outcomes (such as FEV$_1$) between patients receiving TIS with AZM compared with those receiving TIS alone (12). These studies acknowledged key limitations surrounding the nature of retrospective analysis, namely, the limited characterization of patients, unequal subgroups, prior exposure to antimicrobial therapy, and potential for confounding, including by indication.

These studies have served to highlight this unique class-dependent antagonism, but the picture is not entirely clear, and studies of mechanistic pathways are ongoing. Nichols and colleagues demonstrated that the addition of AZM to tobramycin at the same drug concentrations was significantly less effective in bacterial killing using an *in vitro* bacterial aggregation model compared with tobramycin alone ($P < 0.0001$), but did not occur with aztreonam (7). Mechanistically, the MexXY efflux pump in *Pa* is a critical mechanism of adaptive resistance to aminoglycosides, such as tobramycin, and may be activated by ribosomal perturbation occurring in response to antibiotics such as AZM, leading to a form of inducible resistance. AZM induces PA54871, the positive regulator of MexXY, with highest gene activity during combination therapy or directly after an AZM challenge. Finally, as a proof-of-principle experiment, genetic disruption of the MexXY pathway alters this interaction to an additive rather than an antagonistic one (7), adding plausibility to this interaction.

These previously conducted studies, in particular Cogen and colleagues' recent work, highlight several key questions toward the short-term and long-term clinical utility of these agents in combination. Although provocative, the generalizability of these findings needs to be applied carefully to the adult CF population, who are more likely to carry *Pa* and have more episodes of exacerbations, and declining lung function over time requires the addition of increased numbers of therapy to achieve stability. Likewise, we cannot ignore the conflicting evidence of the OPTIMIZE trial, in which potential antagonism did not affect the outcome. Estimating long-term effectiveness of chronic antimicrobial therapy in adults is challenging given the advanced disease states and an existing clinical indication bias toward antimicrobial therapy (13). The benefit of each drug separately (i.e., tobramycin and AZM) has been clearly demonstrated across multiple clinical domains, but initial studies of tobramycin were conducted before prevalent chronic AZM use, the majority of trials have evaluated 6- or 12-month outcomes, and subgroup analysis has not traditionally been conducted to assess for differences between different combinations of therapies (e.g., AZM + chronic tobramycin vs. AZM + chronic colistimethate) (14, 15). The demography and clinical practice in CF have also changed dramatically over the last two decades and the long-term "net effectiveness" of drugs alone and in combination (existing and novel therapies), including potential for adverse drug–drug interactions, needs to be evaluated using contemporary cohorts. On the basis of the concerns of AZM and tobramycin antagonism, a prospective randomized, double-blind, placebo-controlled clinical trial (the TEACH [Testing the Effect of Adding Oral Azithromycin to Inhaled Tobramycin in People With CF] trial; clinicaltrials.gov identifier: NCT02677701) assessing the effect of oral AZM in addition to inhaled tobramycin in patients with chronic *Pa* infection has recently been completed and further discerns the clinical effect in older

patients. Regardless of the outcome, each scenario in which AZM is added to tobramycin, whether during an acute PEx, for eradication, or for chronic maintenance therapy, should be carefully considered and requires evaluation by robust studies.

In conclusion, AZM and tobramycin are commonly prescribed concurrently in both the acute and chronic setting, with combinations occurring in at least half of patients with CF over their lifetime. Both the study in this issue and others before it enforce the concept that "too much of a good thing" may be an accurate adage in select CF populations and that "add-on" therapy should be reevaluated over time. ■

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

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Social Inequities and Cystic Fibrosis Outcomes: We Can Do Better

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Social hierarchy is intuitively recognized by researchers and lay people alike. While one's status in society is easily gauged by professional title, clothing, or residential address, there is not an agreed-upon definition or measure denoting social status. Nevertheless, it cannot be denied that social status is a powerful predictor of health status. At every point across the life course, lower socioeconomic position is associated with poorer health and higher mortality (1–4).

Three possible explanations for the relationship between socioeconomic status (SES) and health should be considered. First, it could be a spurious association resulting from the separate relationships of SES and health outcomes to genetically based factors. For instance, lower intellectual capacity and smaller physical size might lead concurrently to low SES and poor health. Although plausible, this explanation is improbable. In the Whitehall study of mortality (5), for example, the association between job status and health persisted after adjustment for height and body mass index. The second explanation for the association between SES and health status is offered by the health selection (or drift) hypothesis, according to which the association reflects the influence of illness on SES rather than of SES on illness (6). In other words, poverty is a result of poor health, not the other way around. The third explanation of the SES–health relationship is the social causation hypothesis, stating that SES directly and indirectly affects biological functions, which in

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