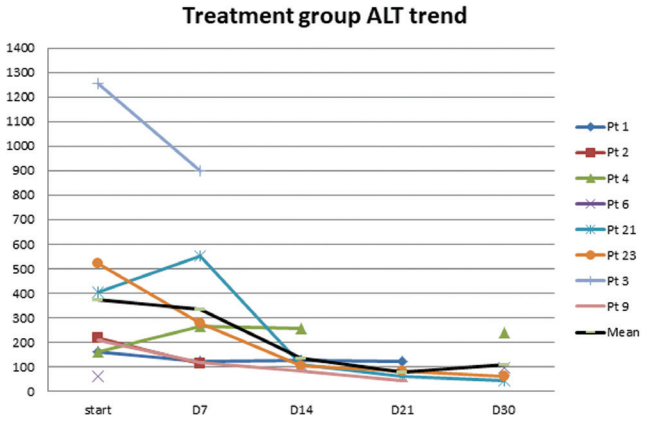

Figure 2.

Disclosures. **All authors:** No reported disclosures.

803. Overcoming β-Lactam Resistance in *Mycobacterium abscessus*

Elizabeth Story-Roller, MD[1] and Gyanu Lamichhane, PhD[2]; [1]Infectious Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland, [2]Johns Hopkins University School of Medicine, Baltimore, Maryland

Session: 70. Tuberculosis and Other Mycobacterial Infections
Thursday, October 4, 2018: 12:30 PM

Background. *Mycobacterium abscessus* (*Mab*) is an environmentally acquired nontuberculous mycobacterium (NTM) that causes severe pulmonary infections in patients with chronic lung disease, such as cystic fibrosis (CF). The incidence of drug-resistant *Mab* infections in CF patients in the United States is steadily rising, making it increasingly difficult to manage these often chronic and incurable infections. *Mab* requires two enzyme classes, L,D- and D,D-transpeptidases, to synthesize peptidoglycan (PG); an integral component of the bacterial cell wall. Each enzyme class is uniquely susceptible to different classes of β-lactam antibiotics. We hypothesize that a combination of two β-lactams, each specific for an enzyme class, will optimally inhibit PG synthesis and swiftly kill *Mab*, with potential to overcome drug-resistance.

Methods. Paired antibiotic combinations were tested *in vitro* for synergy against the *Mab* reference strain ATCC 19977 at 10^6 CFU/mL, per CLSI guidelines. Combinations included two β-lactams, a β-lactam and a β-lactamase inhibitor, or a β-lactam and a rifamycin. The minimum inhibitory concentration (MIC) of each drug was initially confirmed via broth microdilution assay. A validated checkerboard assay was used to determine the fractional inhibitory concentration index (FICI) for each combination to identify pairs that exhibit synergistic activity against *Mab*.

Results. Of the initial 227 combinations screened, 18 pairs exhibited a high level of synergy (FICI ≤ 0.5). Half of these were combinations of two β-lactams. The average reduction in MIC for each drug in combination was at least fourfold, with 8/18 combinations exhibiting reductions greater than eightfold. Although MIC breakpoints against *Mab* have not been established for all of the antibiotics tested in this study, the MICs of at least seven combinations were within the therapeutic range.

Conclusion. Comprehensive inhibition of essential enzymes involved in PG synthesis requires more than one β-lactam antibiotic, and this phenomenon is hypothesized to be the basis for observed synergy between β-lactams. Some of the combinations reduced MICs to within therapeutically achievable levels, potentially leading to vital new treatment options against drug-resistant *Mab.*

Disclosures. **All authors:** No reported disclosures.

804. Impact of Azithromycin Prophylaxis in Lung Transplant Recipients on the Risk of Nontuberculous Mycobacterial Infections

Adrienne Workman, MD[1]; Vaidehi Kaza, MD, MPH[2]; Scott Bennett, MS[1] and Pearlie Chong, MD, MSCR[3]; [1]UT Southwestern, Dallas, Texas, [2]Division of Pulmonary and Critical Care, UT Southwestern, Dallas, Texas, [3]Division of Infectious Diseases, University of Texas Southwestern Medical Center, Dallas, Texas

Session: 70. Tuberculosis and Other Mycobacterial Infections
Thursday, October 4, 2018: 12:30 PM

Background. Azithromycin has been shown to improve FEV1 in lung transplant recipients (LTR) with bronchiolitis obliterans syndrome (BOS). The impact of azithromycin use on the incidence of infections due to *Mycobacterium avium* complex (MAC) and *M. abscessus* in LTR is currently unknown.

Methods. We conducted a nested case–control study of a retrospective cohort of adult LTR transplanted between 2007 and 2017. Cases were defined as LTR with nontuberculous mycobacterial (NTM) infections due to MAC and/or *M. abscessus.* Controls were defined as LTR without NTM infections. NTM infection was defined by presence of pulmonary symptoms and radiographic changes (clinical criteria) in addition to positive cultures from ≥2 sputa or ≥1 bronchial specimens (microbiological criteria) according to the IDSA/ATS criteria. LTR who meet microbiological, but not clinical criteria were considered colonized and not included for analysis. Azithromycin use was defined as ≥90 days for BOS treatment.

Results. Among 538 LTR, 60% (321/538) were male and 81% (434/538) received double LTs. Indication for LT was idiopathic pulmonary fibrosis (28% [152/538]), chronic obstructive pulmonary disease (23% [121/538]), cystic fibrosis [CF] (13% [68/538]), and other (37% [197/538]). The overall incidence of NTM infections was 4.3% (23/538); of which 65.2% (15/23), 17.4% (4/23), and 17.4% (4/23) were due to MAC, *M. abscessus* and polymicrobial infections, respectively. Thirty-one percent (165/538) of LTR received azithromycin. LTR who received azithromycin prophylaxis had 0.21 times the odds of developing NTM infections compared with LTR who did not receive azithromycin prophylaxis (OR: 0.21, 95% CI: 0.02 – 0.86, $P = 0.02$). Age ($P = 0.88$), type of LT ($P = 0.81$), pretransplant NTM colonization ($P = 0.46$), and CF ($P = 0.22$) were evaluated as possible risk factors, but were not associated with increased risk of developing NTM infections in bivariable analyses. In a multivariable logistic regression model, azithromycin prophylaxis was independently associated with decreased risk of NTM infections after adjusting for CF and pretransplant NTM colonization (aOR: 0.20, 95% CI: 0.05–0.88, $P = 0.01$).

Conclusion. Azithromycin use was associated with lower risk of NTM infections due to *M. abscessus* and MAC in our LTR.

Disclosures. **All authors:** No reported disclosures.

805. Amikacin Liposome Inhalation Suspension (ALIS) Add-on Therapy for Refractory *Mycobacterium avium* Complex (MAC) Lung Disease: Effect of *In Vitro* Amikacin Susceptibility on Sputum Culture Conversion

Barbara A.Brown-Elliott, MS, MT(ASCP)SM[1]; Gina Eagle, MD[2]; Richard J. Wallace, MD[1]; Jakko Van Ingen, MD, PhD[3]; Lian J. Pennings, Mr.[3]; Brooke Berry, MBA[4]; Sushil Pandey, PhD, MBA[4]; Chris Coulter, MBBS, FRACP, FRCPA[4]; Melanie Syrmis, PhD[4,5]; Kevin L. Winthrop, MD, MPH[6] and David E. Griffith, MD[1]; [1]University of Texas Health Science Center, Tyler, Texas, [2]Insmed Incorporated, Bridgewater, New Jersey, [3]Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Netherlands, [4]Queensland Mycobacterium Reference Laboratory, Pathology Queensland, Brisbane, Australia, [5]Faculty of Medicine, UQ Centre for Clinical Research, University of Queensland, Brisbane, Australia, [6]School of Public Health, Oregon Health & Science University-PSU, Portland, Oregon

Session: 70. Tuberculosis and Other Mycobacterial Infections
Thursday, October 4, 2018: 12:30 PM

Background. ALIS (590 mg amikacin base) is liposome-encapsulated amikacin for inhalation, which delivers amikacin directly to the lung and limits systemic exposure. In the CONVERT phase 3 trial, significantly more adults with treatment-refractory MAC lung disease receiving ALIS plus guideline-based therapy (GBT) vs. GBT alone achieved sputum culture conversion by month 6 (29.0% vs. 8.9%, $P < 0.0001$). Amikacin treatment failure has previously been reported in patients with amikacin minimum inhibitory concentrations (MIC) >64 µg/mL. We analyzed the impact of amikacin MIC on culture conversion during treatment with add-on ALIS.

Methods. In CONVERT, patients were randomly assigned (2:1) to receive once daily ALIS+GBT ($n = 224$) or GBT alone ($n = 112$). Patients with amikacin-resistant MAC isolates (MICs >64 µg/mL by broth microdilution) were excluded prior to randomization. The primary endpoint was culture conversion, defined as 3 consecutive monthly MAC-negative sputum cultures by month 6. Amikacin MICs were correlated with culture conversion rates.

Results. Amikacin MIC distributions at baseline (day 1) were similar in both groups (Figure 1). Conversion rates in the ALIS+GBT arm were 28.6–34.5% for MAC with amikacin MICs of 8–64 µg/mL (Figure 2). Overall, 28 patients developed post-screening amikacin MIC >64 µg/mL, 4/112 in the GBT alone arm (post-baseline), and 24/224 in the ALIS+GBT arm (1 at baseline and 23 post-baseline after adding ALIS). Most of these (18/24) had MAC isolates with persistent amikacin MIC >64 µg/mL. Only 1/24 patients in the ALIS+GBT arm with amikacin MIC >64 µg/mL achieved culture conversion. No patient with both macrolide resistance and persistent amikacin MIC >64 µg/mL (8/24) converted.

Conclusion. In the ALIS+GBT arm of CONVERT, culture conversion rates were similar for amikacin MICs ranging from 8–64 µg/mL at baseline. Amikacin MIC >64 µg/mL emerged in 10.3% of patients after initiation of add-on ALIS treatment, and 3.6% in the GBT alone arm. Emergent amikacin MIC >64 µg/mL was associated with failure to convert, particularly with concurrent macrolide resistance. Determining amikacin susceptibility at both treatment initiation and during treatment may have utility for guiding treatment decisions.

1. Amikacin MIC Distribution at Baseline, All MAC isolates (ITT Population)