Background. Vancomycin dosing guidelines recommend loading doses (LDs) (25–30 mg/kg TBW), and a maintenance regimen, usually started after a time period equal to the dosing interval. Studies of vancomycin exposure and nephrotoxicity conclude that a 0 to 24-hour area under the serum concentration–time curve (0–24AUC) > 677 mg-hour/L results in a 3- to 4-fold increased risk of nephrotoxicity (Zasowski EJ, Antimicrob Agents Chemother 2018). For vancomycin LDs we compare the calculated LD and the maintenance dose, and delay initiation of the maintenance regimen when the LD exceeds the daily maintenance dose by > 50%. This study assessed the pharmacokinetic outcomes from this technique.

Methods. We retrospectively reviewed 68 consecutive adult patients receiving therapeutic doses of vancomycin. Patient age, sex, height, weight, serum creatinine, and indication were used to calculate the daily dose/intervals for a steady-state 24-hr AUC of 400 or 600 mg-hour/L. The total 0–24AUC was calculated by adding the 0–24 AUC from a 25 mg/kg LD (max: 3 gm) to the 0–24AUC(s) for maintenance dose(s) within the first 24 hours. We compared the total 0-24AUC when the first maintenance dose was timed for the next dosing interval ("scheduled") to that when the maintenance dose was delayed according to our protocol ("delayed"). We tested the proportion of patients who would be exposed to a vancomycin 0-24AUC > 677 mg-hour/L.

Results. 16/68 patients were diagnosed with SSTI (goal 24 hr AUC: 400 mg-hour/L) and 52/68 with sepsis, bacteremia/endocarditis, or pneumonia (24 hr AUC: 600 mg-hour/L). Median daily maintenance dose was 1750 mg (range: 875–4,000 mg). For patients with a goal AUC of 400, the 0-24AUC was > 677 mg-hour/L in one patient using the "scheduled" process and in none of the patients using the "delayed" protocol. However, for patients with a goal AUC of 600, the 0-24AUC was > 677 mg-hour/L in 22/52 patients via the "scheduled" process vs. 4/52 patients via the "delayed" protocol.

Conclusion. For patients with severe gram-positive bacterial infections requiring aggressive dosing of vancomycin, delaying the start of maintenance dosing following a large LD is an effective way to ensure attainment of goal therapeutic AUC within the first 24 hr without placing the patient at increased risk for nephrotoxicity.

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

1577. Particle Characterization of Nebulized Liposomal Amphotericin B and Its Use in the Treatment of Murine Pulmonary Aspergillosis

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Background. Immunocompromised patients are very susceptible to pulmonary aspergillosis causing 50% mortality with present treatments, indicating a need for improved therapy. To address this, we standardized a nebulization method for effectively delivering liposomal amphotericin B (AmBisome®, AmBi) into lungs of Aspergillus fumigatus-infected mice.

Methods. AmBi particle characterization was done with a Cascade particle impactor and a Schuco S5000 nebulizer containing 1.33 mg/mL AmBi. For *in vivo* studies, AmBi was nebulized (neb) into a 12 compartment chamber (one mouse/compartment), following immunosuppression with 28 mg/kg triamcinolone IP (d-3, -1, +1). Mice were challenged d0 with 9 x 10^6 *A. fumigatus* (ATCC#13073) and 4 hours post-challenge, divided into 5 groups (n = 12/gp): 5 days of 20 min/day neb AmBi (Gp1), 5 days of 10 min/day neb AmBi (Gp2), 20 min/day neb AmBi days 0, 1, 3, 5, 7 (Gp 3), 5 days of intravenous(IV) AmBi 7.5 mg/kg/day (Gp4) and IV PBS (Gp5). Seven mice/gp were monitored for survival to d21 and lungs, livers, kidneys, spleens (5 mice/gp) analyzed for mean amphotericin B µg/g and CFU/g.

Results. 87% of neb AmBi particles were between 0.43 mm to 3.3 mm allowing for drug penetration into 1°, 2° and terminal bronchi, bronchioles, and alveoli. This resulted in very good protection, with 20 min daily neb treatments (Gp1) giving 100% survival and 10 min daily neb treatments producing 71% survival (Gp2). There were no survivors in the PBS gp (P < 0.02 vs. Gp1 and Gp2). Every other day neb AmBi or daily IV AmBi was less effective (43% survival). In addition, neb AmBi for 20 min (Gp1) yielded significantly lower fungal burden in lungs vs. all other AmBi treatments (P < 0.02). While drug was detected in lungs of mice given 20 min of neb AmBi (2.6 µg/g), there was no drug detected in livers, kidneys or spleens of any mice given neb AmBi. In comparison, with IV AmBi, drug was detected in the lungs (7 µg/g), livers (204 µg/g), kidneys (38 µg/g), and spleens (114 µg/g).

Conclusion. Daily AmBi nebulization was an effective and potentially less nephrotoxic treatment for murine pulmonary aspergillosis since it achieved significantly lower tissue fungal burden and much better survival vs. daily IV AmBi, without delivering drug to the kidneys.

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

1578. Rifampicin Reduces Tedizolid Concentrations When Co-Administered in Healthy Volunteers

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Background. Tedizolid is an oxazolidinone used to treat skin and soft-tissue infections. Rifampicin is a rifamycin antibiotic which can also treat skin and soft-tissue infections, such as those caused by *Staphylococcus aureus.* Tedizolid and rifampicin could be therefore used concurrently to treat infections. There is currently no clinical data on whether rifampicin affects tedizolid concentrations. Rifampicin is known to be an inducer of cytochrome P450s and transporters. Tedizolid is not known to be cleared by cytochrome P450s, but could be affected by other clearance mechanisms. Therefore we conducted a pharmacokinetic drug-drug interaction study to investigate whether 2 weeks of rifampicin can affect tedizolid concentrations.

Methods. We conducted a healthy volunteer study in 8 subjects. Subjects were first given linezolid 600 mg on day 1, tedizolid 200 mg on day 4, rifampicin 600 mg daily from days 5 to 19 (2 weeks of rifampicin), and an additional dose of tedizolid 200 mg on day 19. Blood was obtained at pre-dose, 1, 2, 3, 4, 5, 6, 8, and 24 hours post dose on days 4 and 19. Concentrations of tedizolid were measured using a validated liquid chromatography / mass spectrometry method.

Pharmacokinetic parameters were calculated by Non-Compartmental Analyses using Phoenix WinNonLin version 8.0. The bioequivalence module was used to obtain ratios of PK parameters pre- and post-rifampicin.

Results. Eight subjects were included in the study. Median age (range) and weight were 34.5 (29–44) years and 64 (58.4–90.8) kg, respectively. Tedizolid was well tolerated in the study. Tedizolid AUC (0–24 hours) was reduced after 2 weeks of rifampicin (GMR 0.80, 90% confidence interval 0.73–0.88), as was Cmin (0.54, 0.44–0.66) and Cmax (0.85, 0.79–0.91). Clearance/F of tedizolid was significantly increased after rifampicin (1.35, 1.21–1.50).

Conclusion. Rifampicin given for 2 weeks has the potential to reduce tedizolid concentrations, especially trough levels, which was reduced by 46%. Caution is recommended when using tedizolid together with rifampicin, especially when tedizolid MIC is high or treating difficult infections.

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

1579. Multidrug-Resistant *Candida auris* Isolates From New York Hospitals and Healthcare Facilities Are Susceptible to Antifungal Combinations

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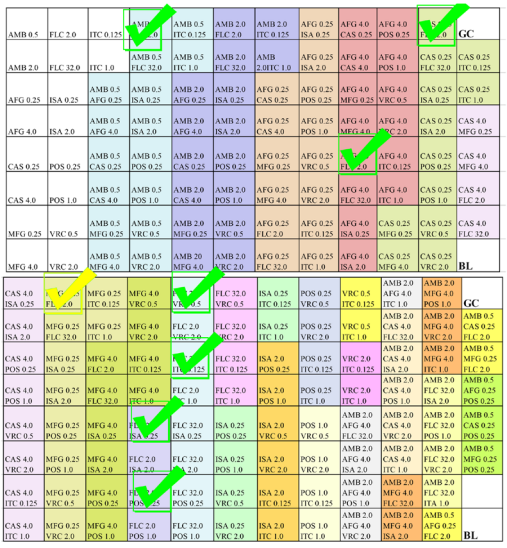
Background. *Candida auris* outbreak continues unabated in New York with the current case counts exceeding 300 patients. We used a modification of standard CLSI broth microdilution method (BMD) if two-drug combinations are efficacious against *C. auris* isolates with high-resistance to fluconazole (FZ, MIC_{50} >256 mg/L), and variable resistance to other broad-spectrum antifungal drugs.

Methods. BMD plates were custom-designed and quality controlled by TREK Diagnostic System. The combination tests of 15 drug-resistant *C. auris* involved microtiter wells with the initial 144 two-drug combinations and their two-fold dilutions (1/2–1/32) to get 864 two-drug combinations finally. We utilized MIC_{100} endpoints for the drug combination readings as reported earlier for the intra- and inter-laboratory agreements obtained against *Candida* species and *Aspergillus fumigatus* (Antimicrob Agents Chemother. 2015. 59:1759–1766). We also tested minimum fungicidal concentrations (MFC).

Results. We tested all possible 864 two-drug antifungal combinations for nine antifungal drugs in use to yield 12,960 MIC_{100} readings, and MFC readings for 15 *C. auris* isolates. Flucytosine (FLC) at 2.0 mg/L potentiated most successful combinations with other drugs. Micafungin (MFG), Anidulafungin (AFG), Caspofungin (CAS) at individual concentrations of 0.25 mg/L combined well with FLC (2.0 mg/L) to yield MIC_{100} for 14, 13, and 12 of 15 *C. auris* isolates tested, respectively. MFG/FLC combination was also fungicidal for 4 of 15 isolates. AMB / FLC (0.25/1.0 mg/L) yielded MIC_{100} for 13 isolates and MFC for three test isolates. Posaconazole (POS), and Isavuconazole (ISA) and Voriconazole (VRC) also combined well with FLC (0.25/2.0 mg/L) to yield MIC_{100} for 12, 13, and 13 isolates, respectively. POS/FLC combination was fungicidal for three isolates.

Conclusion. We identified seven two drug-combinations of antifungals efficacious against drug-resistant *C. auris* strains. The modified BMD combination susceptibility testing could be used by the clinical laboratories to assist providers with the selection of optimal treatment for *C. auris* candidemia.



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