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 (0–24 AUC) > 677 mg·h/L results in a 3- to 4-fold increased risk of nephrotoxicity (Zasowski EL, 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/interval for a steady-state 24 hr AUC of 400 or 600 mg·h/L. The total 0–24 AUC was calculated by adding the 0–24 AUC from a 25 mg/kg LD (max 3 gm) to the 0–24 AUCs for maintenance dose(s) within the first 24 hours. We compared the total 0–24 AUC 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 0–24 AUC > 677 mg·h/L when using the “scheduled” process and in none of the patients using the “delayed” protocol. However, for patients with a goal AUC of 600, the 0–24 AUC was > 677 mg·h/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

Janam J. Dave, MS; Adline Sandoval, MS; Jon Olson, MS; Jill Adler-Moore, PhD; Cal Poly Pomona, Pomona, California, California

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Background. Immunocompromised patients are very susceptible to pulmonary aspergillosis causing 50% mortality with present treatments, indicating a need for novel treatments. 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 use, AmBi was nebulized (nab) into a 12 compartment chamber (one mouse/compart- ment), following immunosuppression with 28 mg/kg triamcinolone IP (d3, -1, +1). Mice were challenged d0 with 9 x 10³ A. fumigatus (ATCC® 10073) and 4 hours post-challenge, divided into 5 groups (n = 12/gp): 5 days of 20 min/day nab AmBi (Gp1), 5 days of 10 min/day nab AmBi (Gp2), 20 min/day nab AmBi (Gp3), 3, 5, 7, 9 days of intravenous (IV) AmBi 7.5 mg/kg/day (Gp4) and IV PBS (Gp5). Seven mice/gp were monitored for survival to day+1 and lungs, livers, kidneys, spleens (5 mice/gp) analyzed for mean amphotericin B µg/g and CFU/g.

Results. 16/68 patients were diagnosed with SSTI (goal 24 hr AUC: 400 mg·h/L and 52/68 with sepsis, bacteremia/endocarditis, or pneumonia (24 hr AUC: 600 mg·h/L). Median daily maintenance dose was 1750 mg (range: 675–4000 mg). For patients with a goal AUC of 400 mg·h/L, the 0–24 AUC was > 677 mg·h/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.

1578. Rifampicin Reduces Tedizolid Concentrations When Co-Administered in Patients With Pulmonary Aspergillosis

Brittany O’Brien, MS; Sudha Chaturvedi, PhD; Vishnu Chaturvedi, PhD; New York State Department of Health Wadsworth Center, Albany, New York

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Background. Candida auris outbreaks continue unabated in New York with the current case counts exceeding 300 patients. We used a modification of standard CLSI broth microdilution method (BMD) to test two-drug combinations are efficacious against C. auris isolates with high resistance to fluconazole (FZ, MIC₉₀ > 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 microtitre 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 MIC₉₀ endpoints for the drug combination testing 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 anti fungal drugs in use to yield 12,960 MIC₉₀ readings, and MFC readings for 15 C. auris isolates. Fluconazole (FLC) at 2.0 mg/L potentiated most successful combinations with other drugs. Micafungin (MFG), Anidulafungin (AFLG), Caspofungin (CAS) at individual concentrations of 0.25 mg/L combined well with FLC (2.0 mg/L) to yield MIC₉₀ for 14, 13, and 12 isolates, respectively. MIC₉₀ and MFC were also fungicidal for 14 of 15 isolates. AMB / FLC (0.25/1.0 mg/L) yielded MIC₉₀ 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 MIC₉₀ for 12, 13, and 11 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.