were approximately 24. This is very similar to previous studies of omadacycline against S. pneumoniae (stasis AUC/MIC 18) and other PK/PD evaluations of tetracycline-class antibiotics. 1-log kill targets were only 2-3 fold more than stasis targets for each strain. This data should provide useful in the dose-regimen optimization of omadacycline.

**Disclosures.** D. R. Andes, Paratek: Grant Investigator, Research support

1532. Human Target Attainment Probabilities for Delafloxacin against Escherichia coli and Pseudomonas aeruginosa

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**Session:** 167. Preclinical Study with New Antibiotics and Antifungals

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**Background.** Delafloxacin (DLX) is a broad-spectrum fluoroquinolone antibiotic under FDA review for the treatment of ABSSSI. Previous studies determined DLX bacterial stasis and 1-log bacterial reduction free AUC_{1,24}/MIC (AUC_{1,24}/MIC) targets for Escherichia coli (EC) and Pseudomonas aeruginosa (PA) in a mouse thigh infection model. The resulting PK/PD targets were used to predict DLX target attainment probabilities (TAP) in humans.

**Methods.** Monte Carlo simulations were used to estimate TAP with DLX 300 mg IV, q12hr. Human DLX plasma pharmacokinetics were determined in patients with ABSSSI in a Phase 3 clinical trial. Individual AUC values were analyzed and determined to be log-normally distributed. The parameters of the AUC distribution were used to simulate random values for AUC_{1,24}, which then were combined with random MIC values based on 2014–2015 US distributions of skin and soft tissue isolates of EC (n = 108) and PA (n = 40), to calculate PK/PD TAPs.

**Results.** DLX/AUC_{1,24}/MIC targets for bacterial stasis and 1-log bacterial reduction for EC were 14.5 and 26.2, and for PA were 3.81 and 5.02, respectively. The Monte Carlo simulations for EC predicted TAPs of 98.7% for stasis at an MIC of 0.25 μg/mL and 99.3% for 1-log bacterial reduction at an MIC of 0.12 μg/mL. The simulations for PA predicted TAPs of 97.3% for stasis and 86.5% for 1-log bacterial reduction at an MIC of 1 μg/mL.

**Conclusion.** DLX 300 mg IV, q12hr, should achieve AUC_{24}/MIC ratios that are adequate to treat ABSSSI caused by most contemporary isolates of EC and PA. For EC, isolates with DLX MICs ≤0.25 μg/mL comprised 73% of all isolates. For PA, isolates with DLX MICs ≤1 μg/mL comprised 88% of all isolates. Similar results would be expected for TAP with oral DLX 450 mg, q12hr.

1534. In Vitro Synergistic Activity of Biapenem Combination with Sulbactam, Collistin, and Fosfomycin Sodium Against Multidrug-resistant Acinetobacter baumannii Isolates from Tertiarycare Hospitals in Thailand

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**Session:** 167. Preclinical Study with New Antibiotics and Antifungals

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**Background.** Acinetobacter baumannii has become a major cause of nosocomial infections worldwide due to highly resistant strains. The use of multidrug-resistant antibiotics is limited by penetration at the site of infection, which have implications for clinical outcomes and emergence of resistance in patients with IAC.

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**Results.** The MICs for MDR- Acinetobacter baumannii were determined according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (2016) by the checkerboard technique. 40 clinical MDR- Acinetobacter baumannii isolates from tertiarycare hospitals in Thailand were tested. The synergistic effect was evaluated by the fractional inhibitory concentration index (FICI).

**Conclusion.** The MIs for MDR- Acinetobacter baumannii results of biapenem and other agents are shown in Figure 1. The FICI results showed all 40 strains (100%) had an FICI < 0.5, suggesting a synergistic effect of colistin in combination with biapenem (Table 1). MIs of mostly strains were decreased two to four doubling dilutions for both antibacterial agents. Moreover, 95% of isolates have MIs to colistin and fosfomycin sodium lower than sensitivity breakpoint when combined with biapenem. The result showed no data on the antagonistic effect (FICI > 4) of all biapenem-based combination.

**Conclusion.** The combination of colistin or fosfomycin sodium with biapenem show synergistic pattern and MIs improvement for all strains. For that reason, the use of colistin, fosfomycin sodium combined with biapenem could be a promising treatment option for MDR- Acinetobacter baumannii.

**FIGURE 1.** MIC for multidrug resistant Acinetobacter baumannii biapenem (n = 63), sulbactam (n = 40), colistin (n = 40), and fosfomycin sodium (n = 40).

| Drug | Sulbactam | Biapenem | Colistin | Fosfomycin Sodium |
|------|-----------|----------|----------|------------------|
| MIC 100 | 100 | 100 | 100 | 100 |
| MIC 50 | 50 | 50 | 50 | 50 |
| MIC 25 | 25 | 25 | 25 | 25 |
| MIC 12.5 | 12.5 | 12.5 | 12.5 | 12.5 |
| MIC 6.25 | 6.25 | 6.25 | 6.25 | 6.25 |
| MIC 3.125 | 3.125 | 3.125 | 3.125 | 3.125 |
| MIC 1.5625 | 1.5625 | 1.5625 | 1.5625 | 1.5625 |
| MIC 0.78125 | 0.78125 | 0.78125 | 0.78125 | 0.78125 |

1533. Unraveling Drug Penetration of Echinocandin Antifungals at the Site of Infection in an Intra-abdominal Abscess Model

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**Session:** 167. Preclinical Study with New Antibiotics and Antifungals

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**Background.** Intra-abdominal candidiasis (IAC) is a prominent invasive fungal infection associated with high mortality. Prompt antifungal therapy and source control are crucial for successful treatment. Echinocandin antifungal drugs are first-line agents. Yet, their clinical effectiveness is highly variable with known potential for breakthrough resistance, and little is known about drug exposure at the site of infection. Using matrix-assisted desorption/ionization (MALDI) mass spectrometry imaging as well as standard analytical techniques, we investigated the spatial and quantitative distribution in tissue lesions for two echinocandins, micafungin and CD101, in a clinically relevant IAC mouse model.

**Methods.** Female 6–8 week old CD1 mice weighing 18–22 g were infected intraperitoneally (IP) with 1 x 10^7 CFU of C. albicans SC5314 mixed with sterile stool matrix. Single IP doses of CD101 at 5 or 20 mg/kg (equivalent to humanized therapeutic dose) or micafungin at 5 mg/kg (therapeutic dose) were administered to mice at day 3 post-inoculation. Mice were sacrificed at just before antifungal treatment (n = 1), and at 1, 3, 6, 24, and 48 hours post-dose (n = 3 per group per time point). Liver and kidney lesions were collected for MALDI imaging. Laser capture microdissection (LCM) followed by liquid chromatography coupled tandem mass spectrometry (LC/MS-MS) was applied to 6 and 24 hours samples for drug exposure measurement. In a separate experiment, mice were treated with 2 or 3 doses of micafungin (5 mg/kg), or a single dose of CD101 (20 mg/kg). Drug accumulation was analyzed at 48 and 72h post the first dose.

**Results.** Drug accumulation within lesions was observed with both drugs at their humanized therapeutic dose. However, micafungin, even at steady-state, failed to approach the mutant prevention concentration (MPC) (16 μg/mL) of the infecting strain. CD101 demonstrated extensive penetration into the lesions after a single dose administration and persisted in lesions at above MPC level of 29.7 μg/mL at 72 hours postdose.

**Conclusion.** These findings indicate that current echinocandin drugs may be limited by penetration at the site of infection, which have implications for clinical outcomes and emergence of resistance in patients with IAC.
**Table 1. Synergistic effect of sulbactam, colistin, and fosfomycin sodium with biapenem against MDR A. baumannii (n = 40) by using the checkerboard assay**

| Effect | Number of Isolates (%) |
|--------|-------------------------|
| Sublactam + Biapenem | Colistin + Biapenem | Fosfomycin sodium + Biapenem |
| Synergy (FIC<0.5) | 30 (75) | 40 (100) | 33 (82.5) |
| Partial synergy (FIC<0.5) | 9 (20) | 0 | 7 (17.5) |
| Additive (FIC=1) | 1 (5) | 0 | 0 |
| Indifference (FIC>1-<4) | 0 | 0 | 0 |
| Antagonism (FIC>4) | 0 | 0 | 0 |

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1535. Nitric Oxide-Releasing Chitosan for the Treatment of Multi-Drug Resistant Superbugs

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**Session:** 167. Preclinical Study with New Antibiotics and Antifungals

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**Background.** Multi-drug resistant superbugs are a serious health threat due to limited treatment options and high mortality rates. Certain superbug strains are now resistant to as many as 36 representative FDA-approved antibiotics, including Colistin and Carbapenem antibiotics, widely considered as the last line of defense against untreatable infections. Nitric oxide (NO) is a diatomic free radical employed by the immune system to eradicate bacteria via oxidative and nitrosative stress. To facilitate storage and controlled release of NO, we have developed NO donor-modified biopolymers based on chitosan, a linear polysaccharide composed of randomly distributed β-linked D-gluosamine and N-acetyl-D-glucosamine. Herein, we report the broad spectrum antibacterial action of low molecular weight (5 kDa) NO-releasing chitosan against Gram-positive and Gram-negative multi-drug-resistant bacterial species, including Klebsiella pneumoniae, Staphylococcus aureus, and Pseudomonas aeruginosa.

**Methods.** MBC assays were performed using CLSI guidelines in a 96-well plate format. All assays were carried out in triplicate using a two-fold dilution range. The bacterial suspension was then diluted in assay medium to a target concentration of approximately 5 × 10⁶ CFU/mL, after which it was added to all test and growth control wells, and allowed to incubate. Test wells were scored for the lowest NO concentration released from the chitosan to inhibit visible growth of the pathogen. After MIC determination, wells demonstrating inhibition were plated, incubated and resulting colonies counted to determine survival concentration. The lowest concentration of NO to inhibit ≥99.9% of a given test organism was reported as the MBC. Of note, chitosan alone had no antibacterial action.

**Results.** MIC and MBC assays for NO-releasing chitosan against six multi-drug resistant strains are provided below.

**Conclusion.** The potencies of the NO-releasing chitosan, including water solubility, make it an excellent drug candidate for treating respiratory infections. Such development is currently underway.

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

1536. Discovery of Antifungal Compounds from Kampo Medicine Against Dermatophytes

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**Session:** 167. Preclinical Study with New Antibiotics and Antifungals

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**Background.** Kampo medicine mainly contain crude extracts of natural products such as plants, animals, and minerals that are prepared according to classical Kampo methodologies. Since plants synthesize numerous antimicrobial components such as plant defensins, Kampo medicine likely contain potent antimicrobial constituents. We have tested antifungal activity of 61 commercially available Kampo medicines by using micro-broth dilution assay with Trichophyton rubrum (T. rubrum), and found that 7 of them had antifungal activity. Among these 7 Kampo medicines 6 contained Ougon which derived from the roots of Scutellaria baicalensis Georgi, and a crude extract of Ougon exhibited significant antifungal activity. This study aims to identify antifungal components contained in Ougon, and determine their antifungal mechanism.

**Methods.** T. rubrum, T. mentagrophytes, Aspergillus fumigatus (A. fumigatus) and Candida albicans (C. albicans) were used for antifungal activity assay. The antifungal activity assay was performed by measuring 595 nm absorbance in micro-broth dilution assay. Active compounds were analyzed by high performance liquid chromatography (HPLC), and identified by liquid chromatography electrospray ionization mass spectrometry (LC-ESI-MS/MS). TUNEL assay, SYTOX-Green Uptake analysis, intracellular reactive oxygen species accumulation assay, mitochondrial membrane potential assay, scanning electron microscopy, and transmission electron microscopy were used to clarify the antifungal mechanism of active components.

**Results.** Upon HPLC analysis, two low molecular weight-components were isolated having potent antifungal activity. The two compounds were identified as Baicalin and Wogonin by LC-ESI-MS/MS. Baicalin showed antifungal activity against T. rubrum, T. mentagrophytes, A. fumigatus and C. albicans. Wogonin showed antifungal activity for all except C. albicans. Detection of antifungal mechanism of Baicalin and Wogonin suggested that their mode of action is apoptosis-like programmed cell death.

**Conclusion.** Baicalin and Wogonin are major compounds to have antifungal activity in Kampo medicine. This study may contribute to the development of new and safe antifungal drugs, especially for the clinical treatment of pathogenic fungal infections.

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1537. Feasibility of Neurapheresis™ as a Therapy for Multidrug Resistant Gram-negative Bacterial Meningitis

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**Session:** 167. Preclinical Study with New Antibiotics and Antifungals

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**Background.** The World Health Organization has identified Pseudomonas, Acinetobacter and Klebsiella (PAK) as three multidrug resistant (MDR) gram-negative pathogens that pose a threat to human health. The greatest threat lies in hospitals, nursing homes, and patients with devices such as intravenous catheters and ventilators. Gram-negative bacterial meningitis (GBM) manifests when these bacteria invade the central nervous system. Due to the threat of increasing antibiotic resistance and the high mortality associated with MDR GBM, we have tested a closed-loop, extracorporeal cerebrospinal fluid (CSF) filtration system (Neurapheresis™) for its applicability in this context. Here we demonstrate feasibility of Neurapheresis for MDR GBM and characterize system parameters for bacterial clearance.

**Methods.** PAK cultures were grown and diluted to 1 × 10⁷ cells/mL in artificial CSF or Luria-Miller broth. Both single pass and closed loop filtration were performed with various tangential flow filtration (TFF) and dead-end filter paradigms. Samples were taken either immediately post-filter or after every full CSF volume cycle (150 mL) during a long-term closed loop experiment. Bacterial load, endotoxin and cytokines were quantified.

**Results.** In single pass tests, 5kDa and 100kDa TFF filters with 0.2µm and 0.45µm dead-end filters excluded all PAK bacterial isolates completely. The 100kDa and 5kDa TFF filters significantly reduced endotoxin concentration by >95% and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>-99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL10). In closed-loop experiments, both TFF filters significantly reduced endotoxin concentration by >95% and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL10). In closed-loop experiments, both TFF filters significantly reduced endotoxin concentration by >95%, and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL10). In closed-loop experiments, both TFF filters significantly reduced endotoxin concentration by >95% and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL10). In closed-loop experiments, both TFF filters significantly reduced endotoxin concentration by >95%, and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL10). In closed-loop experiments, both TFF filters significantly reduced endotoxin concentration by >95% and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL10). In closed-loop experiments, both TFF filters significantly reduced endotoxin concentration by >95% and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL10). In closed-loop experiments, both TFF filters significantly reduced endotoxin concentration by >95% and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL10). In closed-loop experiments, both TFF filters significantly reduced endotoxin concentration by >95% and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL10). In closed-loop experiments, both TFF filters significantly reduced endotoxin concentration by >95% and >99% of baseline, respectively. The 5 kDa TFF filters produced a 2-log (>99%) reduction in cytokines (IL-1ra, IL-6, TNF, CRP, and CXCL10). In closed-loop experiments, both TFF filters significantly reduced endo...