Table 1: FURI Outcomes by Fungal Disease

	N	Complete or Partial Response, Clinical Improvement N (%)	Stable Response N (%)	Progression of Disease N (%)	Indeterminate N (%)
Invasive Candidiasis					
Candidemia	11	8 (72.7%)	1 (9.0%)	1 (9.0%)	1 (9.0%)
Intra-abdominal infections	14	7 (50%)	3(21.4%)	2 (14.2%)	1 (7.1%)
Bone/joint	8	5 (62.5%)	2 (25%)		1 (12.5%)
Urinary tract infection	1		1 (100%)		
Subcutaneous wound infection	2	2 (100%)			
Mediastinitis	1	1 (100%)			
Empyema	1	1 (100%)			
Endocarditis	1	1 (100%)			
Mucocutaneous Candidiasis					
Oropharyngeal candidiasis	14	9 (64.3%)	3 (21.4%)	2 (14.3%)	
Esophageal candidiasis	10	6 (60%)	4 (40%)		
Vulvovaginal candidiasis	7	5 (71.4%)	1 (14.3%)		1 (14.3%)
Chronic mucocutaneous candidiasis-skin	1		1 (100%)		
Invasive Aspergillosis					
Pulmonary	3	2 (66.7%)	1 (33.3%)		

1 Death, not related to fungal disease

Methods. FURI patients were eligible for enrollment if they have proven or probable, severe mucocutaneous candidiasis, invasive candidiasis or invasive aspergillosis,other fungal diseases and evidence of failure to, intolerance to, or toxicity related to a currently approved standard-of-care antifungal treatment or can not receive approved oral antifungal options (e.g., susceptibility of the organism) and a continued IV antifungal therapy is clinically undesirable or unfeasible.

Results. An independent Data Review Committee (DRC) provided an assessment of treatment response for 74 patients enrolled in the FURI study from 22 centers in US, UK and EU treated with ibrexafungerp for mucocutaneous or invasive fungal infections from 2016- 2020. A total of 39 (52.7%) patients had invasive candidiasis, 32 (43.2%) had mucocutaneous candidiasis and 3 (4.5%) patients had invasive aspergillosis. The percent of patients who were determined to have a complete response (CR), partial response (PR), clinical improvement (CI) was 63.5%, stable disease (SD) was 23.0%, patients with progression of disease 6.8% and 4 patients were indeterminate. Additionally, there was 1 death in the FURI study that was not related to fungal disease. Table 1 shows outcomes by fungal disease type as determined by the DRC.

Conclusion. Analysis of 74 patients from the FURI study indicates that oral ibrexafungerp provides a favorable therapeutic response in patients with challenging fungal disease and limited treatment options.

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124. Establishment of a Post-Influenza Aspergillosis Model in Corticosteroid-Immunosuppressed Mice

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Session: O-25. New Findings in Medical Mycology

Background. Post-influenza aspergillosis (PIA) is a feared complication in patients with severe influenza, especially those receiving corticosteroids. However, validated murine models of PIA in a background of corticosteroid immunosuppression are lacking, compounding efforts to better characterize the immunopathology and treatment of this emerging entity.

Methods. 8-week-old female BALB/c mice were infected with ~5% of the lethal dose of a mouse-adapted influenza A/Hong Kong/1968 (H3N2) strain (flu), delivered by aerosolization, versus control (aerosolized saline). Mice then received two intraperitoneal injections of 10 mg cortisone acetate (CA) or mock injections on days 5 and 8 after flu infection. On day 9, mice were intranasally challenged with 50,000 *A. fumigatus* AF-293 conidia or mock-infected with

saline. Survival was monitored until day 16 and infection severity was scored using the modified murine sepsis score (MSS, 0 = healthy to 3 = moribund). Pulmonary fungal burden was determined by an 18S quantitative PCR assay on day 16 or upon death. 15-16 mice per group were assessed across 3 independent experiments.

Results. Flu infection alone caused modest early morbidity, followed by full recovery of the mice until day 16. Treatment with CA after flu infection led to 12% mortality and increased morbidity that persisted until day 16 (median MSS = 0.8). Similarly, mice infected with AF after CA treatment had 12% mortality and a median MSS of 0.7. Combination of all 3 challenges (flu, CA, and AF) led to 40% mortality and severe morbidity in surviving mice (median MSS = 2.7). Likewise, prior flu infection of CA-treated, AF-infected mice increased the pulmonary fungal burden from 27k to 80k median conidial equivalents. In contrast, mice not receiving CA treatment showed consistently low morbidity (median day-16 MSS = 0.5) and minimal fungal burden after AF challenge, regardless of prior flu infection.

Conclusion. We have established a model of PIA in CA-immunosuppressed mice that underscores the detrimental effect of corticosteroid therapy on the outcomes of PIA. In the future, we will employ this model to study the impact of various pharmacological interventions on the natural history of PIA in the background of corticosteroid immunosuppression.

Disclosures. **Dimitrios P. Kontoyiannis, MD**, **Astellas** (Consultant)**Cidara Therapeutics** (Advisor or Review Panel member)**Gilead Sciences** (Consultant, Grant/Research Support, Other Financial or Material Support, Honoraria)

125. Dynamic PET facilitated Pharmacokinetic Modeling and High-dose Rifampin Regimens for *Staphylococcus aureus* Orthopedic Implant Associated Infections: Bench to Bedside

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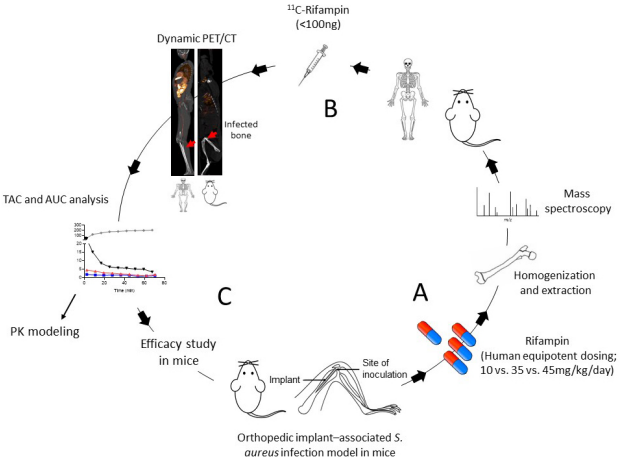
Session: O-26. New Insights into Microbial Pathogenesis

Background. Rifampin, has potent, dose-dependent sterilizing activity against Gram-positive bacteria with the area under the concentration-time curve (AUC) being the most predictive of bactericidal activity. Combination therapy with rifampin (10-15 mg/kg/day) is recommended to treat *S. aureus* orthopedic implant associated infections. Recently, high-dose rifampin (35 mg/kg/day) has been shown to be safe in humans and is being evaluated to shorten tuberculosis treatments.

Methods. Dynamic ^{11}C-rifampin (chemically identical to rifampin) positron emission tomography (PET) was used to determine rifampin bone exposures (AUC) in mice and patients with *S. aureus* bone infection (**Figure 1**). PET data facilitated a pharmacokinetic model to predict rifampin concentration-time profiles in bone tissues, which were used to design studies in a mouse model of *S. aureus* orthopedic implant infection utilizing advanced imaging.

Figure 1. Experimental schematics.



(A) A validated mouse model of S. aureus orthopedic implant associated infection was used to determine bone concentrations following administration of escalating rifampin oral dosing (human equipotent dosing is indicated). m/z, mass/charge ratio. (B) Human patients and mice with S. aureus orthopedic infection were imaged using 11C-rifampin PET / CT. PET signal was quantified in infected and uninfected bone to generate time-activity curves (TACs) used to calculate area under the concentration time curve (AUC) over 45-90 minutes. These data were used to develop a pharmacokinetic model to predict rifampin exposures in bone. (C) Efficacy studies in mice compared vancomycin alone to vancomycin with either standard-dose or high-dose rifampin. Readouts included weekly in vivo bioluminescence, bacterial load and broth cultures at completion of follow up and CT to evaluate adverse bone remodeling. Bacterial isolates were evaluated for phenotypic resistance as well as subjected to whole genome sequencing. Human studies were approved by the Johns Hopkins University Institutional Review Board Committee. Patients were prospectively recruited at the Johns Hopkins Hospital and 11C-rifampin PET was performed under the U.S. FDA Radioactive Drug Research Committee program guidelines for investigational drugs. Animal studies were approved by the Johns Hopkins Animal Care and Use Committee. Approvals from the Johns Hopkins Biosafety, and Radiation Safety were also obtained for all studies.

Results. ^{11}C-Rifampin PET median bone to plasma AUC ratio was 0.14 (IQR 0.09 – 0.19) in patients (**Figure 2A-E**), lower than previously reported using single time-point measures. Pharmacokinetic simulations and tissue measurements demonstrated that administration of high-dose rifampin leads to substantial increases in bone tissue concentrations (**Figure 2F-G**). Importantly, 4-weeks of high-dose rifampin administered in combination with vancomycin was non-inferior to the 6-weeks combination treatment with standard dose rifampin and vancomycin, recommended by the IDSA [risk difference: -6.7% (-20% – 6.9%) favoring high-dose rifampin] (**Figure 3**). Finally, high dose rifampin ameliorated antimicrobial resistance (0% vs 40%; $P = 0.04$), genetic alterations related to persistence (whole-genome bacterial sequencing) (**Figure 4A-B**) and mitigated adverse bone remodeling (high-resolution computed tomography) (**Figure 4C-D**).