inner colonies within the zone of inhibition around the fosfomycin disk confounds interpretation of susceptibility testing. The goal of this study was to estimate the frequency of these non-susceptible inner colony E. coli mutants and to identify their resistance mechanisms.

Methods. Disk diffusion testing of fosfomycin was performed on 650 E. coli clinical isolates at UMPC between 2011 and 2015 (496 were ESBL-producing). For E. coli strains producing inner colonies within a non-susceptible zone of inhibition (≤12–15 mm in diameter), disk diffusion testing was repeated to confirm that stable resistance had developed. Both the parental strains and their corresponding most proximal inner colony mutants were subjected to MIC testing, whole-genome sequencing, qRT-PCR, and carbohydrate utilization studies.

Results. Of the 650 E. coli clinical isolates, 6 (0.9%) produced non-susceptible inner colonies. Whole-genome sequencing revealed deletions of uhpA and uhpC, respectively. Both genes are required for expression of uhpT. Carbohydrate utilization showed that all six inner colony mutants had decreased growth on minimal medium supplemented with glucose-6-phosphate compared with their parent strains. Expression of uhpT was absent in the mutant strains with deletions of uhpT and lower in mutants with mutations of uhpC and uhpA compared with their parents by qRT-PCR.

Conclusion. Among E. coli clinical isolates studied, occurrence of non-susceptible inner colonies within the zone of inhibition around the fosfomycin disk confounds susceptibility testing. All six mutants contained functionally defective uhpT, which accounted for the resistance.

Disclosures. All authors: No reported disclosures.

32.2. The Gastrointestinal Tract Is A Major Source of Echinocandin Drug Resistance in a Candida glabrata Colonization Model

Kelly Healey, PhD; Yanan Zhao, MD; Yoji Nagasaki, MD; Steven Park, M.S.; Carlota Medus, PhD, MPH; Louise François Watkins, MPH; Marita S. Karlsson, PhD; Sandra Boyd, BS; Vivian Leung, MD; Alycia McNutt, BS; Carlota Medus, PhD; MPH; Xiong Wang, DVM, PhD; Samir Hanna, MD; Jielu Zhang, MPH; Ana Colón, MPH; Anna Barringer, CPH; Cheryl Dunbar-Manley, BSN, RN; John Timberlake, PhD; Stuart G. Seeger, MD; Kelley Healey, PhD

Session: 51. Emerging Resistance – Epidemiology and Mechanisms
Thursday, October 5, 2017: 12:30 PM

Background. Gastrointestinal (GI) Candida commensals may be a major source of invasive candidiasis and a hidden reservoir of antifungal resistance. Candida glabrata resistance rates for increased greater than those of other species. Herein, we present a C. glabrata GI colonization model to explore how antifungal drugs affect resistance acquisition and systemic breakthrough infections.

Methods. Immunocompetent mice were treated with antibiotics to clear native GI bacteria and then inoculated via gavage with C. glabrata. Fecal samples were collected throughout the study to assess fungal GI colonization. Daily administration of caspofungin (CSF; 5 or 20 mg/kg i.p.), synthein inhibitor nikkomycin Z (Nz; 100 mg/kg oral), or saline was initiated on day 3 post inoculation. CSF-resistant colony frequencies were determined through selection of fecal samples on CSF-supplemented media, and FKS mutations were identified using the newly developed molecular beacon diagnostic assays. Dexamethasone was administered to induce immunosuppression. Upon completion of the experiment, blood, and organs were harvested and yeast burden levels determined.

Results. Daily therapeutic dosing (5 mg/kg) of CSF resulted in no reduction in fecal burdens, little resistance (0-10%), and organ breakthrough rates similar to control groups. Treatment with high dose (20 mg/kg) CSF caused a ≥2.5-log decrease in average burden, yet high levels (10/10 mice) of resistance (≥12/12 mutants) were observed following 9 days of treatment. Although breakthrough rates decreased in this group, yeast recovered from organs contained ≤3 mutations. The largest reduction (3 log) in GI burdens was obtained within 3–5 days of high dose CSF plus Nz (100 mg/kg oral) treatment. However, echinocandin resistance was again observed from all mice (10/10) following 5–7 days of treatment. Treatment with the therapeutic dose plus Nz left GI burdens unchanged, but did significantly reduce organ breakthrough rates (20%; P < 0.05).

Conclusion. We have developed a C. glabrata GI colonization and dissemination model. Systemic breakthrough depends on both gut C. glabrata population composition and serum/tissue drug level.

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323. Genomic Pathways Associated with Daptomycin (DAP) Resistance in DAP-Susceptible Enterococcus faecium Harboring Substitutions in LiaFSR

Truc T. Tran, PharmD; Lorena Diaz, PhD; Rafael Rios, MSc; An Dinh, BS; Sayeedahameen Jahanabakhsh, PharmD; Razieh Rehbari, PharmD; Michael J. Rybak, PharmD, MPH; PhD and Cesar Arias, MD, PhD, FIDSA; 1Department of Internal Medicine, University of Texas McGovern Medical School at Houston, Houston, Texas; 2Molecular Genetics and Antimicrobial Resistance Unit - International Center for Microbial Genomics, Universidad El Bosque, Bogota, Colombia; 3Anti-Infective Research Laboratory, Department of Pharmacy Practice, Wayne State University, Eugene Applebaum College of Pharmacy & Health Sciences, Detroit, Michigan

Session: 51. Emerging Resistance – Epidemiology and Mechanisms
Thursday, October 5, 2017: 12:30 PM

Background. DAP is used off-label for treatment of severe enterococcal infections. DAP resistance (R) in E. faecium has been associated with changes in LiaFSR, a three-component regulatory system that controls the cell envelope stress response to antibiotics. In particular, substitutions in LiaS (T120A) and LiaR (W73C) seem to predispose to development of DAP-R during therapy, without increasing the DAP MIC above the clinical breakpoint. Using a PK/PD model of simulated endocardial vegetations, we evaluated the genomic pathways for DAP-R under different DAP dose schemes.

Methods. A DAP-susceptible E. faecium (HOU503; MIC 3 μg/ml) harboring the LiaS substitution was subjected to simulated doses of 6, 8, and 10 μg/kg in the model for 14 days using a starting inoculum of 10⁶ CFU/ml. Sixteen DAP-R isolates were recovered from the SEV model: five isolates from 6 μg/kg (D6 isolates from days 2 to 4); five isolates from 8 μg/kg (D8 isolates from days 2 to 8); and six isolates from 10 μg/kg (D10 isolates from days 1 to 14) which were subjected to whole genome sequencing. Reads from each sequenced isolate were mapped against the HOU503 genome for SNP analyses. Variant calling was done with GATK, SamTools, and the low-frequency variant detector from CLC Genomics Workbench 8.5. Variants detected by the three callers were selected and annotated with SnpEff, then compared among the different groups of isolates accordingly to the DAP doses that were exposed.

Results. We detected a total of 16 proteins exhibiting substitutions consistently in all the DAP-R sequenced isolates; including mobile genetic elements (9), hypothetical proteins (2), β-lactamase, a putative adhesin, a β-acetylglucosamine-specific PTS system, a β-N-acetylmannosamine-6-phosphate 2-epimerase and a MurR/RpR, which is a transcriptional regulator that represses the operon MurPQ involved in the uptake and degradation of N-acetylmuramic acid. Notably, mutations in carbohydrate synthase were prevalent only in isolates recovered under D8 dose. The LiaRS substitutions remained in all isolates.

Conclusion. Using a humanized SEV PK/PD model and SNP-based analyses, we were able to uncover possible novel genetic pathways associated with the development of DAP-R via the LiaFSR system in enterococci.

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324. Emergence of mcr-1 among Nontyphoidal Salmonella Isolates in the United States

Louise Francois Watkins, MPH; Jason Folster, PhD; Jessica Chen, PhD; Maria S. Karlsson, PhD; Sandra Boyd, BS; Vivian Leung, MD; Alycia McNutt, BS; Carlota Medus, PhD; MPH; Xiong Wang, DVM, PhD; Samir Hanna, MD; Jielu Zhang, MPH; Ana Colón, MPH; Anna Barringer, CPH; Cheryl Dunbar-Manley, BSN, RN; John Timberlake, PhD; Stuart G. Seeger, MD; Kelley Healey, PhD

Session: 51. Emerging Resistance – Epidemiology and Mechanisms
Thursday, October 5, 2017: 12:30 PM

Background. Colistin is considered a critically important antimicrobial for its role in the treatment of severe multidrug-resistant infections. Colistin resistance conferred by the plasmid-mediated gene mcr-1 has been reported in enteric pathogens globally since 2015, but remains rare in the United States. We describe the search for mcr-1 among nontyphoidal Salmonella (NTS) and the identification of the first human cases in the United States.

Methods. Whole genome sequencing (WGS) was performed on NTS isolates from humans by state health departments, from retail meat by the US Food and Drug Administration, and from food animals by the US Department of Agriculture. Sequences were uploaded to the National Center for Biotechnology Information and screened through their pathogen detection pipeline for the presence of resistance determinants (including mcr-1) beginning in late 2015; screening included some retrospective sequences. Isolates with the suspected mcr-1 gene were submitted to CDC for confirmatory PCR. Epidemiological information on human cases was collected from state health departments.

Results. Over 70,000 Salmonella isolates from humans, retail meat, and food animals were screened for mcr-1. No NTS with mcr-1 were identified in retail meat or food animals. Four human cases of NTS with mcr-1 were identified by WGS and three were confirmed by PCR (1 pending testing): Salmonella Corvallis in an 18-year-old man from Tennessee (isolation July 2014), Salmonella Enteritidis in a 55-year-old woman from Connecticut (isolation May 2016), Salmonella Typhimurium in a 57-year-old woman from Virginia (isolation November 2016), and Salmonella Enteritidis in a 47-year-old man from Minnesota (isolation April 2017). All patients traveled internationally in the 10 days prior to illness onset.

Conclusion. NTS rarely contain mcr-1 in the United States. To date, all human cases have been linked to international travel, reflecting the higher prevalence of mcr-1 reported from other parts of the world. The absence of mcr-1 in NTS from US food animals and retail meat is likely because colistin has not been used in food production.