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 UPMC 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 deletion of uhpT in 4 of the E. coli strain inner colonies, while the remaining two strains contained non-sense mutations in 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 colony mutants was rare. All six mutants contained functionally defective uhpT, which accounted for the resistance.

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

Keller, Philip D.; Yanan Zhao, MD; Yot Nogasaki, MD; Steven Park, M.S.; Steven Park, M.S.; David Perlin, PhD; Public Health Research Institute, New York Medical College, New York, New York

**Session:** 51. Emerging Resistance – Epidemiology and Mechanisms

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**Background.** Gastrointestinal (GI) Candida commensals may be a major source of invasive candidiasis and a hidden reservoir of antifungal resistance. Candida glabrata has increasingly greater threat to Candida species compared to 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. Mice were inoculated via oral gavage with C. glabrata. Fecal samples were collected throughout the study to assess fungal GI colonization. Daily administration of capsaicin (CSF; 5 or 20 mg/kg i.p.), chitin synthase 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 reduced burden 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 (10-100 mice) of resistance (9/12/mutants) were observed following 9 days of treatment. Although breakthrough rates decreased in this group, yeast recovered from organs contained Kx 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 mice) following 9-57 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, PharmD1; Lorena Diaz, PhD2; Rafael Rios, MSc2; An Dinh, BS3; Sreydhamaneh Jabahabgh, PharmD2; Razeh Rehbiem, PharmD2; Michael J. Rybak, PharmD, MPH2; and Cesar Arias, MD, PhD, FIDSA1,2; Department of Internal Medicine, University of Texas McGovern Medical School at Houston, Houston, Texas, 1Molecular 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

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**Background.** DAP is used off-label for treatment of severe enterococcal infections. DAP resistance 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 mg/ml) harboring the LiaS allele was subjected to simulated 3× MIC DAP schemes. Within the LiaS (T120A) and LiaR (W73C) mutant strains, the following DAP dose schemes were tested: 6× MIC DAP for 48 h, 1× MIC DAP for 7 days, followed by 6× MIC DAP for 1 day, and 1× MIC DAP for 7 days. The LiaS 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, MD, MPH1; Jason Folster, PhD2; Jessica Chen, PhD3; Maria S. Karlsson, PhD3; Sandra Boyd, BS1; Vivian Leung, MD1; Alycia McNutt, BS1; Carlota Medus, PhD, MPH4; Xiong Wang, DVM, PhD5; Samir Hanna, MD6; Aliah Halil Smith, DVM6; MPH1; Anna Barringer, CPH1,2; Cheryl Dunbar-Manley, BSN, RN1,7; Janita Balk, BSN, RN1,8 and Cindy Friedman, MD, Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; 3Centers for Disease Control and Prevention, Atlanta, Georgia; 4IHRC, Inc., Atlanta, Georgia; 5Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; 6Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; 7Connecticut Department of Public Health, Hartford, Connecticut; 8Minnesota Department of Health, St. Paul, Minnesota; 9Tennessee Department of Health, Nashville, Tennessee; 10Virginia Department of Health, Richmond, Virginia

**Session:** 51. Emerging Resistance – Epidemiology and Mechanisms

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**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 Typhimurium in a 57-year-old woman from Virginia (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
animal agriculture in the United States, underscoring the importance of a One Health approach to combat antimicrobial resistance.

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325. Lack of Fosfomycin Resistance in Commensal E. coli after Fosfomycin Treatment
Robert P. Matsu, BS; Serena Kantz, BS; Sarah Bowler, BS; Christi McElhenny, MS; Anthony Pasculle, ScD; and Yuhao Dui, MD, PhD; University of Pennsylvania School of Medicine, Pittsburgh, Pennsylvania; University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

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Background. Fosfomycin (fos) is active against Enterobacteriaceae coli and approved for treatment of uncomplicated urinary tract infection (UTI). FOS-resistant E. coli mutants can easily be seen in vitro, but FOS resistance is not widespread among clinical isolates of E. coli to date. It is not known whether FOS leads to development of FOS resistance in commensal E. coli.

Methods. Patients who were admitted FOS were prospectively identified at a teaching hospital in Pennsylvania between January 2016 and February 2017. Weekly perirectal swabs from these patients that were routinely collected for screening of VRE colonization were retrieved. The swabs were first suspended in nutrient broth for enrichment for 4 hours, followed by overnight culture on EMB agar plates with or without 10 µg/ml of FOS and 25 µg/ml glucose-6-phosphate. The limit of detection was 10 CFU/swab.

Results. During the 12-month study period, 552 doses of FOS were given to 505 patients. We recovered and tested 501 swabs from 283 of these patients. Among them, 105 patients showed colonies collected before and after their FOS dose. Colonies consistent with E. coli grew in 106 of 501 swabs tested, 44 of which were collected after FOS administration. However, none of them grew E. coli with reduced FOS susceptibility.

Conclusion. The finding suggests that either intestinal exposure to oral FOS does not facilitate generation of FOS resistance among commensal E. coli, or such FOS-resistant mutants may be generated but are competed out due to reduced fitness.

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326. β-Lactamase Characterization of Baseline Pseudomonas aeruginosa (PSA) from Five Ceftazidime-Avibactam (CAZ-AVI) Phase 3 Clinical Trials
Brendan R. E. Morgan, MD; Maria Mariana Castanheira, PhD; Andrea K. Cardin, MD; Gregory G. Stone, PhD; Robert Mclaughlin, PhD; Patricia Bradford, PhD; and Robert K. Flamm, PhD; JMI Laboratories, Inc., North Liberty, Iowa; Formerly of AstraZeneca Pharmaceuticals LP; Waltham, Massachusetts; AstraZeneca, Waltham, Massachusetts

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Background. CAZ-AVI has been evaluated in Phase 3 trials for the treatment of complicated urinary tract infections, complicated intra-abdominal infections, and hospital-acquired pneumonia, including ventilator-associated pneumonia. This study presents the β-lactamate characterization of baseline PSA recovered from patients enrolled in five Phase 3 trials of CAZ-AVI.

Methods. ISAB baseline PSA isolates (one per patient) were included (19 countries). Isolates met the β-lactamate MIC screening criteria, and displayed CAZ MIC ≥16 µg/ml and/or carbapenem MIC 28 µg/ml. Susceptibility (S) testing was centrally performed by CLSI methods. Isolates underwent microarray-based assay, PCR/ sequencing for screening of ESBL and carbapenemases (CARB), and qRT-PCR for these carbapenemase-resistant genes detected. Colonies consistent with E. coli grew in 106 of 501 swabs tested, 44 of which were collected after FOS administration. However, none of them grew E. coli with reduced FOS susceptibility.

Conclusion. The finding suggests that either intestinal exposure to oral FOS does not facilitate generation of FOS resistance among commensal E. coli, or such FOS-resistant mutants may be generated but are competed out due to reduced fitness.

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327. The Association of mRNA Expression of Cell Wall Biosynthesis-Related Genes and the Reversion to Daptomycin (DAP) Susceptibility in DAP Non-Susceptible Methicillin-Resistant Staphylococcus aureus
Takayoshi Iwata, MD, PhD; Ken Ito, MD, PhD; and Robert K. Flamm, PhD; JMI Laboratories, Inc., North Liberty, Iowa; AstraZeneca: Research Contractor, Research grant

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Background. Daptomycin (DAP) is widely used in the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infection. The emergence of DAP non-susceptible MRSA strains during therapy is a major concern in clinical settings. However, it is not clear whether DAP non-susceptible MRSA has the ability to revert to a susceptible strain.

Methods. We obtained an MRSA strain pair, DAP non-susceptible strain and subsequent DAP susceptible strain, from a patient. To understand the underlying mechanism by which DAP non-susceptible MRSA reverts to a susceptible strain, we performed genetic and phenotypic analysis in the strain pair.

Results. Although whole-genome analysis revealed four missense mutations, including L826F in mpfR, in both strains, the net cell-surface charge was similar between the DAP non-susceptible and susceptible strains. However, the thickness of the cell wall was higher in the DAP non-susceptible strain, which was decreased to the same level as the control after reversion to the DAP susceptible strain. Moreover, the non-susceptible strain showed higher mRNA expression of the two-component system (TCS), such as VraSR, yapC and GraS, with the up-regulated transcription levels of cell-wall biosynthesis-related genes. The expression levels of those genes were decreased after reversion to the susceptible strain.

Conclusion. These results indicated that DAP non-susceptibility due to up-regulation of the TCS and cell-wall biosynthesis-related genes may be reversible by the discontinuation of DAP leading to reversion to the DAP susceptible phenotype.

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328. Dominance of a macrolide-resistant lineage resulting from capsular switching among group B Streptococcus invasive disease in non-pregnant adults in Portugal (2009–2015)
Elisia Lopes, MSc; Tana Fernandes, MSc; Miguel P Machado, MSc; João Arraio, PhD; José Melo-Cristino, PhD; and Alexandre Anjos, PhD; and Portuguese Group for the Study of Streptococcal Infections; 1Instituto De Microbiologia, Instituto De Medicina Molecular, Faculdade de Medicina, Universidade De Lisboa, Lisbon, Portugal

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Background. Lancefield group B streptococci (GBS) are increasing as a cause of invasive disease among non-pregnant adults. We set out to characterize GBS isolated from non-pregnant adults in Portugal in 2015.

Methods. All GBS isolates (n = 555) were serotyped, assigned to clonal complexes (CCs) by multilocus sequence typing and characterized by surface protein and pilus islands (PI) gene profiling. Antimicrobial susceptibility testing was done by disk diffusion. Resistance genes were identified by PCR. High-throughput sequencing of representative isolates was performed.

Results. Overall, serotype Ia was the most frequently found in the population (31%), followed by serotypes Ib (24%), Ib, V (18%), and III (13%). Serotype Ib increased significantly over the study period for the Ib, V and III serotypes (P < 0.001), to become the most frequent serotype after 2013. Over 40% of the isolates belonged to CC1, including most isolates of serotypes Ib (n = 110) and V (n = 65), all sharing surface protein gene alp3 and PI-1+PI-2a. Overall erythromycin and cindacinicam resistance rates were 35 and 34%, respectively, both increasing throughout 2009–2015 (P < 0.01). Macrolide resistance was associated with CC1 (P < 0.001) and serotype Ib (P < 0.001). Genomic analysis revealed that the Ib/CCI lineage probably resulted from the acquisition of the type Ib capsular operon in a single large recombination event (≈300 Kb) by a representative of the V/CCI macrolide-resistant lineage.

Conclusion. The serotype Ib/CCI genetic lineage was detected for the first time and expanded in Portugal in the last 6 years and is now dominant among the GBS population causing invasive disease in adults.

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329. Sustained In Vitro Activity of Linezolid and Eliciting Resistance Mechanisms: Summary of the Zyxov® Annual Appraisal of Potency and Spectrum Program for 2016
Rodrigo E. Mendes, PhD; Patricia A. Hogan, MBA; Mariana Castanheira, PhD; Helén S. Sader, MD, PhD; and Robert K. Flamm, PhD; JMI Laboratories, Inc., North Liberty, Iowa; Pfizer Inc., Collegeville, Pennsylvania

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Background. Linezolid (Zyxov®) is an FDA approved drug for the treatment of infections due to organisms in the genera Enterococcus, Staphylococcus, and Gram-positive bacteria, including pathogens resistant to other available antibiotics.

Methods. The Linezolid In Vitro Activity (LIVA) program is a prospective, uncontrolled, open-label, single-arm study. The LIVA program included in vitro susceptibility testing performed by CLSI methods and analysis of the potential molecular mechanisms of resistance.

Results. In total, 58/189 (30.7%) CAZ-S PSA were selected due to high MIC results for carbapenem and ESBL enzymes, and 22.9% (30/131) had no susceptibility. Among CAZ-nonS PSA (69.3%; 131/189), 45.8% (60/131) showed overexpression of AVI resistant (R) and 36.5% (19/52) of these carried metallo-β-lactamases; 12 isoforms of these enzymes (CARB) and displayed CAZ MIC >32 µg/ml. In addition, 15% (30/131) were positive for the VIM-2 β-lactamase gene in a single large recombination event (≈300 Kb) by a representative of the V/CC1 macrolide-resistant lineage.

Conclusion. These results indicated that DAP non-susceptibility due to up-regulation of the TCS and cell-wall biosynthesis-related genes may be reversible by the discontinuation of DAP leading to reversion to the DAP susceptible phenotype.

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