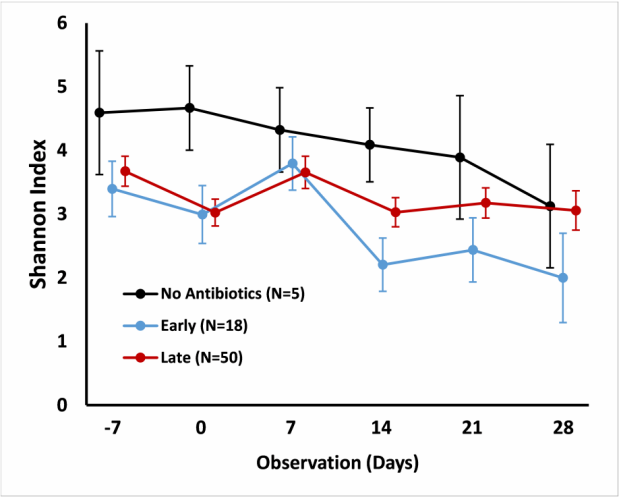
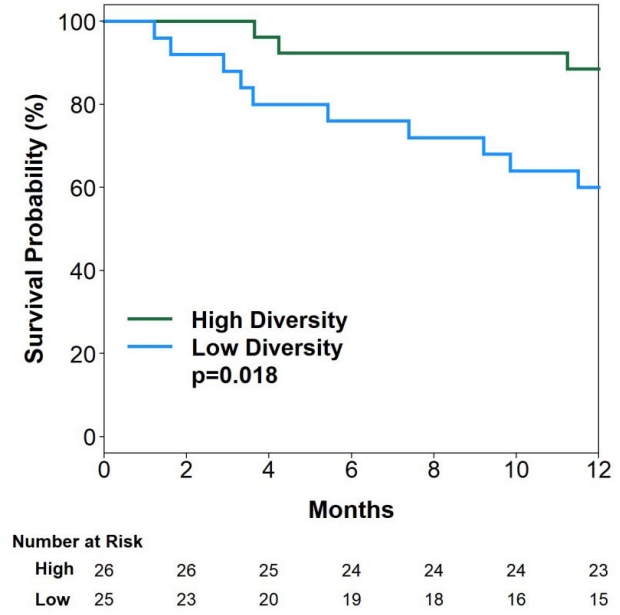


Figure 2. One-year overall survival of patients with high (>2.77) versus low (<2.77) diversity defined by median Shannon-Index.

Conclusion. We have shown a significant correlation between engraftment microbiome diversity and 1-year OS. Early antibiotic exposure was detrimental to microbiome diversity. Approaches to preserve microbiome diversity and prevent BSI are likely to improve HCT outcomes. Our ongoing trial using rifaximin will provide preliminary data regarding this approach.



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

42. Common Population Variants Cause Susceptibility to Disseminated Coccidioidomycosis

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Session: O-9. Basic and Translational Science

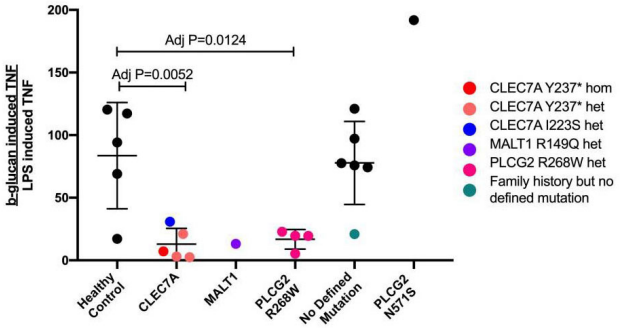
Background. *Coccidioides* are endemic, dimorphic fungi found in soils of southwestern United States, Mexico and Central America. Infection occurs via inhalation of arthroconidia which swell, differentiate into spherules and rupture releasing endospores. While the majority of infected individuals will never report illness, roughly 1/3 seek medical attention for fungal pneumonia and ~1% of those present with disseminated coccidioidomycosis (DCM). IL12-IFNγ pathway mutations have been reported in DCM but are exceedingly rare and cannot account for the ~500–600 cases of DCM/year.

Methods. We performed whole exome sequencing on 66 individuals with DCM, retaining variants predicted damaging (CADD >15) with a population frequency < 10%.

Results. Homozygous *CLEC7A* c.714T >G; p.Y238* causing a truncated Dectin-1 receptor was overrepresented (OR=9.8449, 95% CI 3.0841 to 31.4260, P=0.0001). Dectin-1 signaling pathway variants included 3 homozygous and 11 heterozygous *CLEC7A* p.Y238* individuals, one each *CLEC7A* p.I223S and *MALT1* p.R149Q and five *PLCG2* p.R268W. Since Dectin-1 is the receptor for b-glucan, a major *Coccidioides* cell-wall component, we hypothesized that Dectin-1 pathway variants could affect fungal recognition and cellular response. Healthy control PBMCs stimulated with purified β-glucan or heat-killed *Candida albicans* induced 6-fold more TNFα than patients with homozygous or heterozygous *CLEC7A*, *PLCG2* or *MALT1* variants (P=0.0022, Ordinary one-way ANOVA). Additionally, one patient with a family history of DCM but lacking a defined mutation also failed to up-regulate TNFα after stimulation.

Normalized TNF production from healthy control and DCM patient's peripheral blood mononuclear cells

Conclusion.



These data are consonant with increased dissemination in *Clec7a*$^{-/-}$ mice as well as in patients receiving anti-TNF biologics. These gene variants accounted for 31% of our DCM cohort (21/66 patients). This is the first demonstration of variants outside the IL12-IFNg pathway impairing fungal recognition and cellular response in coccidioidomycosis. Common heterozygous variants may be sufficient for disease susceptibility to highly pathogenic organisms.

Disclosures. **Michail Lionakis, MD, ScD**, **Matinas BioPharma** (Research Grant or Support)

43. The Capsule and Beyond: Genetic Determinants of Pediatric streptococcus Pneumoniae empyema

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Session: O-9. Basic and Translational Science

Background. *Streptococcus pneumoniae* is the most common cause of pneumonia in children, including empyema, a severe complication with increasing incidence in the post-pneumococcal vaccine era. Only a subset of > 90 serotypes cause empyema. Virulence determinants of empyema remain largely unknown.

Methods. We performed Illumina sequencing of invasive Pneumococcal isolates from pediatric patients at Primary Children's Hospital (Salt Lake City, UT) isolated between 1996–2018, *de novo* genome assembly (SPADES), annotation (PROKKA), serotyping (Quelling and SeroBA), and pan-genome assembly (ROARY). SCOARY and pyseer were used for microbial GWAS. Maximum likelihood phylogeny was calculated using RAxML/Gubbins.

Results. 366 pneumococcal isolates were analyzed from 39 serotypes and multiple phenotypes including pneumonia (n=76), empyema (n=63), CNS infection (n=54), and isolated bacteremia (n=79). Serotypes and empyema phenotype clustered roughly by phylogeny. Most analyzed empyema isolates after 2010 were serotype 3 (19/25); prior to PCV-13 introduction serotypes 1 (8/38), 7F (7/38), and 19A (11/38) were more highly represented. Genes implicated in capsule synthesis, transposases, and metabolism were statistically correlated with the empyema phenotype.

Conclusion. Specific capsular or metabolic genes may confer optimal fitness for pleural disease. Further characterization of these genetic associations is needed and will inform future treatment and prevention.

Disclosures. **Carrie L. Byington, MD**, **BioFire** (Other Financial or Material Support, Royalties for Intellectual Property)**IDbyDNA** (Advisor or Review Panel member) **Krow Ampofo, MBChB**, **Merck** (Grant/Research Support)

44. In-host Infection Dynamics Of Pseudomonas Aeruginosa Pneumonia

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Session: O-9. Basic and Translational Science

Background. *Pseudomonas aeruginosa* (PA) is an important cause of healthcare-associated infections including pneumonia and bloodstream infections (bacteremia). PA pneumonia is a significant cause of morbidity and mortality, especially in immunocompromised patients and those on prolonged mechanical ventilation; However, little is known about the in-host infection dynamics of PA pneumonia and its relationship to transmission.

Methods. We utilized a mouse model in conjunction with sequencing technology to dissect the infection dynamics of PA pneumonia. BALB/c mice were challenged intranasally with a clinical isolate, PABL012. At various time points post infection, organs were harvested and the surviving PA enumerated. STAMP (sequence tag-based analysis of microbial populations) analysis was applied to define the in-host infection dynamics.

Results. Bacterial enumeration revealed that PA disseminates early and widely in intranasally infected animals. Infected mice shed significant amounts of PA in their gastrointestinal tract (GI). Finally, STAMP analysis revealed that compared to bloodstream infections where PA experiences a severe *in vivo* bottleneck when trafficking to GI tract, PA disseminates freely from the lungs to the GI tract with little bottleneck effect.

Conclusion. Our research, using murine models, sheds light on the infection dynamics of PA pneumonia. Our results suggest that the lungs are a unique environment in which PA replicates unchecked and experiences little bottleneck effect. This unchecked replication likely seeds the gastrointestinal tract and promotes significant fecal excretion. Fecal excretion of PA from hospitalized patients is observed, but the direct link between pneumonia, GI shedding, and transmission remains unclear. Our observations have significant implications for infection control and shed light on how PA might exit the human host into the healthcare environment setting the stage for a transmission event.

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

45. In Silico Identification of Virulence Factors That May Contribute to Enhanced Gut Colonization of ESBL e. Coli

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Session: O-9. Basic and Translational Science

Background. The rapid global spread of extended spectrum beta lactamase-producing *Escherichia coli* (ESBL-E) strains threatens our ability to the treat many common infections and have become a major threat to public health. Some ESBL-E have a fitness advantage allowing them a competitive edge in gut colonization contributing to their global spread. We aimed to conduct *in silico* molecular characterization of virulence factors that may contribute to this fitness advantage.

Methods. For this observational study, we report data from fifteen whole-genome sequenced ESBL-E isolates found in the stool of a cohort of otherwise healthy infants. These strains were compared to MG1655 (commensal E. coli) and UTI89 (pan-sensitive uropathogenic E. coli). Phenotypic growth curves were done in minimal media with glucose as the only carbohydrate source. The genome sequences were assembled and annotated using Pathosystems Resource Integration Center (PATRIC) database and used to predict antibiotic resistance genes (ARGs) as well as virulence factors that may be driving the competitive advantage of these strains.

Results. All ESBL E. coli strains encoded multiple ARGs including those that target beta-lactams, aminoglycosides, fluoroquinolones, tetracyclines and macrolides. Growth curves in minimal media showed enhanced growth of some ESBL E. coli compared to control strains (Figure 1). ESBL-E strains 7 and 8 were also shown to have a higher copy number of carbohydrate metabolism genes. Proteome comparison of ESBL-E to MG1655 or UTI89 identified 93 and 321 proteins, respectively, with < 50% homology to the corresponding protein in the comparator strains (Figure 2). However, only 29 proteins across all ESBL-E were showed non-homology to both MG1655 and UTI89. These included both fimbrial and phosphotransferase system proteins.

Figure 1

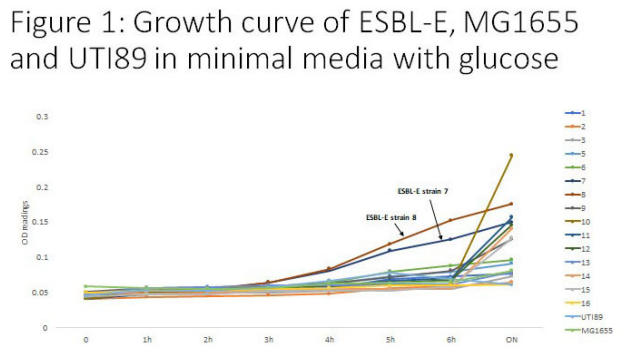


Figure 2A

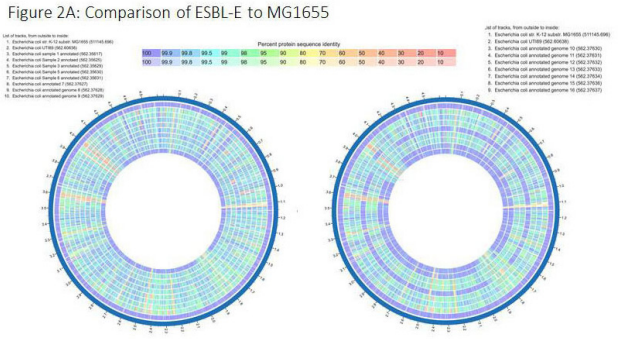
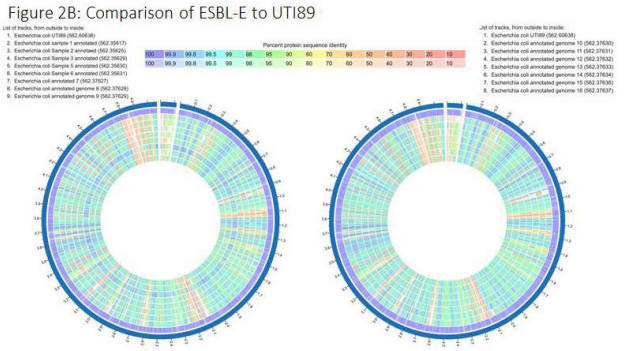


Figure 2B

Conclusion. ESBL-E strains may use a combination of attributes to out-compete commensal or non-resistant E. coli. These may include enhanced carbohydrate metabolism, increased adherence to the epithelial cells (via fimbrial proteins) or greater efficiency of carbohydrate uptake from the environment (via the phosphotransferase system). Further *in vitro* and *in vivo* studies are in progress to verify these *in silico* observations.



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

46. Tacrolimus Increases Susceptibility to Secondary Infection in a Mouse Model

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Session: O-9. Basic and Translational Science

Background. Transplant acceptance requires life-long pharmacological intervention that broadly suppresses recipients' immunity in order to prevent rejection of foreign graft. In turn, non-specific immune-suppression in these patients is also associated with increased risk of infection from opportunistic pathogens. Currently our knowledge on the effects immune suppressive therapies on adaptive immune components response in patients is limited

Methods. To investigate this we established a mouse model of post-transplant immune suppression therapy, using tacrolimus. To dissect the effects of tacrolimus on infection susceptibility, tacrolimus-treated mice were infected with a virulent strain of recombinant Listeria monocytogenes (Lm) expressing model antigens. Infection with this transgenic strain of Lm transforms these model antigens into surrogate Lm antigens and allows tracking of pathogen-specific T-cells using MHC tetramer staining.

Results. Here we show, tacrolimus treatment triggered increased susceptibility to secondary, but not primary Lm infection with increased bacterial burden in the liver and spleen tissues. Increased susceptibility during secondary infection paralleled dampened functional activation of Lm-specific CD8+ T cells as indicated by diminished in vivo cytolytic activity. Interestingly, when tacrolimus treatment was initiated only during primary or during secondary infection susceptibility to infection was overturned as both groups of mice had lower bacterial burden in target tissues. This suggests that while tacrolimus treatment does not negatively impact primary immune response, it may dampen the formation of CD8+ T cell memory.

Conclusion. Further studies will investigate the long-term durability of blunted pathogen-specific memory and CTL activity triggered by tacrolimus treatment after cessation of therapy. These findings will allow more defined prediction of patient risk of infection allowing for a personalized prophylaxis regimen.

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