Session: O-9. Basic and Translational Science

Background. *Pseudomonas aeruginosa* (PA) is an important cause of health-care-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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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 1: Growth curve of ESBL-E, MG1655 and UTI89 in minimal media with glucose

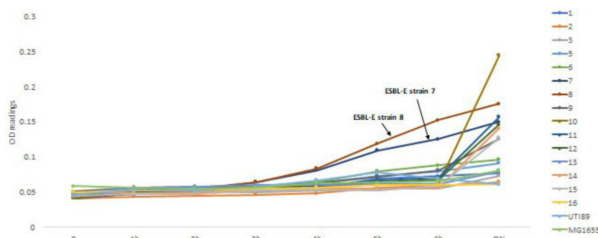


Figure 2A

Figure 2A: Comparison of ESBL-E to MG1655

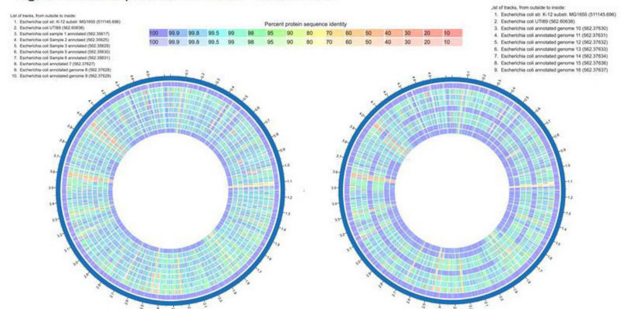
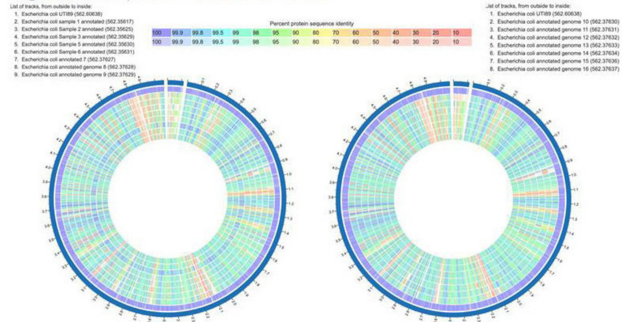


Figure 2B

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.

Figure 2B: Comparison of ESBL-E to UTI89



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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