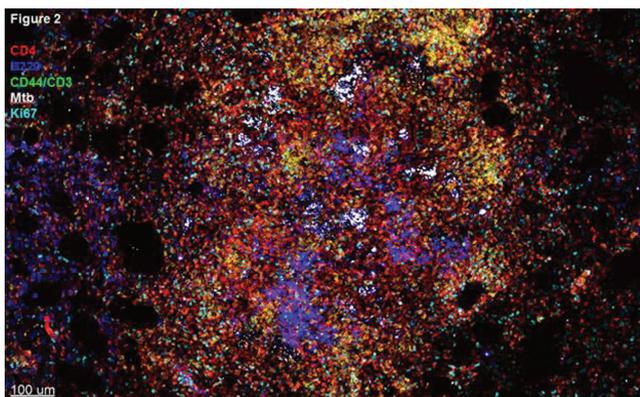
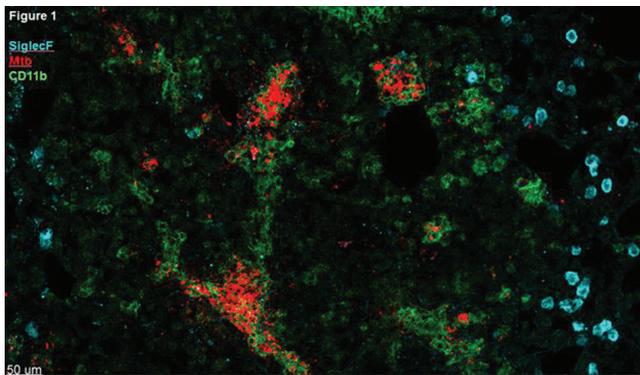


Background. Mycobacterium tuberculosis (*M.tb*) is the leading infectious cause of mortality; however, there is no vaccine that confers lasting protection. To investigate the immune response to *M.tb*, we have developed an ultra-low dose (ULD) infection model in mice that better reflects the heterogeneous outcomes of human infection. Additionally, we have identified a blood transcriptional signature, taken at day 24, that predicts future bacterial burden after day 70.

Methods. Mice were infected with an ULD (1–3 CFU) of H37Rv *M.tb*. Control mice were infected with 50–100 CFU. Blood was drawn at day 24 for RNA signature. At early (day 34–35), and late (day 82–83) time points, mice were injected with an intravascular label. Individual lungs were then assessed for bacterial burden, phenotypic and spatial analysis of immune cells by flow cytometry, and histocytometry, a type of immunohistochemistry that allows for imaging of >12 colors

Results. At day 35, the following cell populations were correlated with an RNA signature score predicting disease progression: ESAT-6 tetramer+ CD4+ T cells ($R^2 = 0.35, P < 0.01$), TB10.4 tetramer+ CD8+ T cells ($R^2 = 0.34, P < 0.01$), and B cells ($R^2 = 0.28, p = 0.01$) within the lung parenchyma, as well as CD11b+ cells, negative for CD64, Ly6c, Ly6g and MHCII ($R^2 = 0.38, p < 0.01$) within the lung vasculature. These same populations were correlated with elevated CFU at day 83, as well as dendritic cells ($R^2 = 0.53, p < 0.01$). No populations were correlated with a protective RNA score. We have observed the complex spatial organization of granulomas while optimizing our histocytometry panel. This includes infected macrophages (Fig 1) interdigitated with B cell aggregates, associated with naïve T cells, interspersed with CD44+ T cells, with diffuse staining for Ki67, suggestive of tertiary lymphoid structures (Figure 2).

Conclusion. This model replicates heterogeneity of TB seen in humans, while also providing a way to correlate differences in the immune response to future outcome. We have associated distinct immune cell subsets with the failure to control TB. With a larger sample size and data from histocytometry, we will have improved resolution to discern protective elements of the immune response to TB, which we can then test mechanistically in our model.



Disclosures. All authors: No reported disclosures.

1765. Strain-level Determination of the Contribution of Gut Microbiota to the Development of Bacteremia in Patients Undergoing Stem Cell Transplantation

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Background. Infection is a major preventable cause of transplant-related morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HCT). Bacteremia is the most common infectious complication in HCT, often occurring during periods of mucositis when the risk for microbial translocation from the intestine is increased. Prior research in HCT patients using 16S rRNA sequencing demonstrated that gut microbiota dominance by either *Enterococcus* spp. or Proteobacteria was associated with the development of bacteremia with *Enterococcus* spp. and Gram-negative organisms, respectively. No studies to date, however, have compared bacteremia isolates and gut microbiota samples at a strain-specific level using next-generation shotgun metagenomic sequencing (NGS).

Methods. In order to assess the degree of genetic similarity between bacteremia isolates and the gut microbiota, we identified patients who had undergone HCT at Stanford and developed a bacteremia between October 2015 and September 2016 for whom we had both saved blood culture isolates and stool samples within 30 days preceding bacteremia. We identified 15 patients from whom we had 17 bacteremia isolates, and performed NGS (Illumina HiSeq 4000) on stool and isolate DNA. We generated draft assemblies of isolate genomes using the SPAdes assembler, and aligned stool metagenomic reads to the draft isolate genomes using Bowtie2, filtering reads for perfect end-to-end alignment.

Results. Enteric gram-negative bacteremia isolates were identical to those in the gut microbiota, as has been demonstrated in prior studies using older strain-typing **Methods.** Surprisingly, we also identified gram-positive organisms that were identical in both the blood and stool prior to bacteremia, which challenges existing dogma regarding sources of gram-positive bacteremia-causing organisms.

Conclusion. Using a highly sensitive and accurate NGS-based strain typing method, we provide evidence of translocation of organisms from the gut microbiota and subsequent bacteremia. The gut was confirmed as a source for both classic enteric gram-negative and classically non-enteric Gram-positive bacteremia in HCT patients. These findings may have implications for the origins of bacteremia in HCT patients previously classified as CLABSIs.

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1766. The Gut Microbiota of Healthy Infants in the Community is a Reservoir for ESBL and Carbapenemase Producing Bacteria.

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Background. The recent rapid rise of Extended-spectrum B Lactamase producing Gram-negative bacteria (ESBL-GNB) has seriously threatened the treatment of common infectious diseases. Neonates have an immature immune system and a delay in appropriate treatment due to ESBL-GNB sepsis can be fatal. This problem of delayed therapy is magnified in the developing world where 99% of the deaths from community acquired neonatal sepsis occur. Additionally ESBL *E. coli* such as the strain ST131 are known to be persistent gut and vaginal colonizers. In animal models, these strains out-compete colonization with drug-sensitive, commensal *E. coli*. Gut colonization with ESBL-GNB in infants may therefore have a profound impact on their microbiome and increase their risk of sepsis. Pakistan is a lower middle income country with high antibiotic use per capita and a sharp increase in ESBL-GNB infections. Recent data show that >50% of *E. coli* isolates from reproductive-aged women of Pakistan are resistant to more than one class of antibiotics. We aimed to determine the rates of gut colonization with ESBL-GNB among healthy infants in a community setting.

Methods. Stool samples were collected from 100 healthy infants living in a Pakistani suburban community between the ages of 5 and 7 months. Samples were plated on MacConkey agar to select for Gram-negative bacteria. Isolates were screened for resistance against several antimicrobial classes. Molecular testing of the stool samples was done using primers targeting conserved regions of ESBL and carbapenemase genes.

Results. Forty-eight percent of the infants were positive for ESBL producing Gram-negative bacteria, the majority of which were *E. coli*, and 7.5% were positive for carbapenemase producers, all of which belonged to *Klebsiella* spp. Molecular testing showed that 85% of the infant stools were positive for TEM β -lactamase gene, 68% for the CTX-M β -lactamase gene and 33% for the KPC carbapenemase gene.

Conclusion. The widespread colonization of infants in a developing country with ESBL-GNB is highly concerning. Further, our studies have revealed that the resistome of otherwise healthy infants may be a major reservoir of antibiotic genes in the community. Gut microbiome analysis of the potential impact of colonization with antibiotic-resistant bacteria is on-going.

Disclosures. All authors: No reported disclosures.

1767. Longitudinal Comparison of the Microbiota During *Klebsiella pneumoniae* Carbapenemase-Producing *Klebsiella pneumoniae* (KPC-Kp) Acquisition in Long-Term Acute Care Hospital (LTACH) patients

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