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9050, an instrumented blood culture system. The platelet count and prothrombin time were performed using Abacus Junior5 hematology analyzer and i-STAT 1 analyzer respectively. Of the 231 neonates hospitalised with clinical sepsis, blood culture reports were positive in 51 cases (21.4%). Klebsiella spp. (35.3%) and Staphylococcus aureus (27.5%) were the most common Gram-negative and Gram-positive isolates respectively. Thrombocytopenia was observed in 30(58.8%) of the neonates with septicemia. Of the 9(17.6%) patients with severe thrombocytopenia, seven (77.8%) had Klebsiella spp. septicemia. Out of the 21(63.6%) of thrombocytopenia produced by Gram-negative isolate, 17(80.9) had increased prothrombin time. In conclusion, Gram-negative organisms showed the highest cases of severe thrombocytopenia and prolonged PT. This study has helped to establish a disturbance in hemostatic systems in neonates with septicemia. Further studies, however, may be required to assess other hemostasis parameters in order to understand their interaction with the infectious organisms in neonates.

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NEW SIGNALING PATHWAYS AND METABOLITES FOR HOST:PATHOGEN COMMUNICATION DURING GASTROINTESTINAL INFECTIONS

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Background: Precise and regulated activation and production of bacterial virulence factors during gastrointestinal infection is a critical determinant for diarrhea. Signaling molecules, receptors, downstream regulators and in vivo spatiotemporal expression kinetics for several virulence factors, and subsequent host responses to infections are also not properly understood and defined. These processes can serve as targets for prophylactic and therapeutic interventions against infectious diseases. **Findings:** We report discovery of several bacteria two-component signaling pathways (TCS) and their cognate signals (host metabolites), which regulate toxin production in Vibrio cholerae and other enteric bacteria by mutually exclusive and novel non-canonical mechanisms. We also report two novel high-throughput and systems-biology portable assays to measure host and bacterial RNA expression profiles and metabolites of infected mice, and generate a "molecular signature" of diarrheal diseases. We first utilized high-throughput screening to identify bacterial TCS pathways regulating cholera toxin production, followed by genomics, digital gene-expression technology, RNA-Seq, metabolomics, proteomics and animal models to decipher their detailed mechanism. One TCS pathway acts a phosphorylation-mediated switch between bacterial virulence gene expression and host metabolism. It activates bacterial toxin production during hypoxia via a non-phosphorylated response regulator, and represses host metabolic process detrimental to pathogenesis in it's phosphorylated form. A second TCS pathway senses host potassium levels, and activates toxin production via tyrosine phosphorylation of its response regulator. Thus, this pathway can switch between aspartate and tyrosine phosphorylation of its cognate response regulator to modulate bacterial virulence and pathogenesis. Using sequencing and 2D LC/ESI/MS/MS proteomics, I identify protein-interacting partners and DNA binding sites of these TCS. By characterizing a battery of locked, null, constitutively actively genetic point mutants under standard laboratory conditions, followed by profiling spatiotemporal kinetics of host immunity and metabolism regulated by these pathway using digital gene-expression technology and high-throughput metabolomics in a mouse model, I confirm phenotypes and mechanisms of these signaling modalities. **Significance:** My data integrates bacterial signaling and host responses in vivo to identify a new landscape of host-pathogen interactions, metabolites and mechanisms for infectious diseases. I also report two novel RNA and metabolic profiling approaches that

can be ported into systems-biology platforms, which will have wide utility in microbiology research.

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MICROBIAL INTERACTIONS AND EVOLUTION IN CHRONIC CYSTIC FIBROSIS INFECTIONS

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Chronic cystic fibrosis (CF) airway infections provide opportunities for fundamental investigations related to microbial evolutionary dynamics, diversity, and interactions within a natural polymicrobial ecosystem. Patients with CF are predisposed to airway infections from a wide range of microbial species of which Pseudomonas aeruginosa is the major contributor to patient morbidity and mortality. It is well-established that diverse factors such as the host defense, antibiotic treatment in the clinic, and a heterogeneous distribution of nutrients drive P. aeruginosa evolutionary adaptation to the lung environment. However, whether interactions with other infecting microbes is also an evolutionary driver is not well understood. To begin to explore the relationship between evolution and microbial interactions, we have focused on two distinct P. aeruginosa lineages (called "DK1" and "DK2") that have transmitted among and evolved in CF patients in Denmark during the last 40 years. Although most patients are infected with either clone-type, DK1 and DK2 have also been co-existing in many patients for extended periods. Here, we focused on a single patient with a mixed infection containing both clone types. To investigate interactions between DK1 and DK2 we sequenced the genomes of isolates sampled from the patient over 15 years. Surprisingly, we identified isolates with mosaic genomes: These isolates (which we call "DK1/2") had DK2-based genomes but containing regions of DK1 DNA acquired by horizontal gene transfer and recombination. DK2 isolates are sensitive towards R5 pyocins produced by other P. aeruginosa lineages. We show that the transferred regions provide enhanced R5 pyocin resistance to DK1/2. Our data suggest that the within-host genetic interactions between co-infecting DK1 and DK2 strains could be driven by super-infections with R5 producing genotypes. To more systematically explore interactions between DK1 and DK2, we are mapping phenotypic interactions between 100 DK1 and DK2 isolates sampled from multiple patients. For that purpose we are currently performing a pairwise screening on agar surfaces using differentially fluorescent-tagged strains to assess neutral, negative or positive effect. Our results point towards an unexplored area for novel interference treatment strategies in relation to microbe-microbe interactions.

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WITHIN-HOST EVOLUTION OF PSEUDOMONAS AERUGINOSA TOWARD IRON ACQUISITION FROM HEMOGLOBIN IN POLYMICROBIAL CF INFECTIONS

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Bacterial pathogens require iron to survive and colonize a human host but their access to free iron is often limited by iron-withholding process where free iron is bound by proteins such as hemoglobin. Although most pathogens have developed tactics to acquire iron from host proteins, little is known about how evolutionary processes modulate bacterial iron acquisition systems in chronic, polymicrobial infections where interspecies competition for limited iron could be an evolutionary driver. To begin to address this issue, we use chronic airway infections in patients with cystic fibrosis (CF) as a model to investigate evolutionary adaptation to an iron-limited environment in a polymicrobial context. Here, we investigate the within-host evolution of the transmissible P. aeruginosa DK2 lineage sampled from (CF) airway infections over a period of