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2018. Host Gene Expression Classifiers Distinguish Bacterial and Viral Infections in Sri Lankan Patients with Acute Febrile Respiratory Illness

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Background. Acute febrile illness is a frequent cause of hospitalization in the tropics and often presents with respiratory symptoms, even when caused by non-respiratory pathogens. Previously, host-based gene expression signatures accurately identified acute respiratory infections as being bacterial or viral in a U.S. cohort. We determined signature performance in a Sri Lankan cohort with acute febrile respiratory illness (AFRI).

Methods. We enrolled patients with AFRI in Sri Lanka from July 2012 to May 2013 and collected nasopharyngeal swabs, acute/ convalescent sera, and blood in PAXgene RNA tubes. Bacterial (Orientia tsutsugamushi, Leptospira spp.) and viral (influenza A/B, dengue) infections were confirmed using polymerase chain reaction, virus isolation, enzyme immunoassay, and/or microscopic agglutination testing. We extracted total RNA and performed host RNA sequencing (illumina). We aligned reads to high reference genome using Bowtie2, quantified at isoform level using Express version 1.5.1, and normalized using trimmed-mean normalization. The original model estimated three classes and separate signatures predicted bacterial infections, viral infections, and non-infectious illnesses. Regularized regression was used to predict bacterial and viral infections based on prior signatures. Accuracy was estimated using leave-one-out cross-validation.

Results. Among 43 patients with viral infections (14 dengue, 29 influenza) and 16 patients with bacterial infections (six Leptospira spp., 10 O. tsutsugamushi), median age was 21 years (IQ: 13–31) and 49% were male. Of five respiratory symptoms (cough, sore throat, rhinitis/ congestion, shortness of breath, and pain with breathing), median (Q3R) number of symptoms was 2 (1–2) for influenza, 2 (1–2) for dengue, 2 (2–3) for Leptospira spp., and 1.5 (1–2) for O. tsutsugamushi. We observed high predictive accuracy in discriminating bacterial and viral infections: AUROC 0.91 for the bacterial and AUROC 0.81 for the viral model. At enrollment, 65% of viral and 50% of bacterial AFRI patients received antibiotics.

Conclusion. Host gene expression classifiers performed well in a Sri Lankan population with AFRI, even with nonrespiratory pathogens that may not be readily identified. Host-based diagnostics may play a critical role in improving diagnostic ability and antibiotic use globally.