Host Gene Expression Classifiers Distinguish Bacterial and Viral Infections in Sri Lankan Patients

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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 [1].

Prevalently, host-based gene expression signatures accurately identified acute respiratory infections as being viral or in a US cohort [2].

Phenotyping
• We enrolled patients with AFRI in Sri Lanka from July 2012-May 2013 and collected nasopharyngeal swabs, acute and 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.

Genomic expression
• We extracted total RNA and performed host RNA sequencing (Illumina). We aligned reads to hg38 reference genome using Bowtie2, quantified at isoform level using Express version 1.5.1, and normalized using trimmed-mean normalization. The original model estimated 3 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.

Methods
• Among 43 patients with viral infections (14 dengue, 29 influenza) and 16 patients with bacterial infections (6 Leptospira spp, 10 O. tsutsugamushi), median age was 37 years (IQR 23-51) and 40% were male.

Of 5 respiratory symptoms assessed (cough, sore throat, rhinitis/congestion, shortness of breath, and pain with breathing), median (IQR) 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.

Results
• 5 of 8 symptom sets were strongly associated with viral infections, 2 symptom sets with bacterial infections, and 1 symptom set with both viral and bacterial infections. AUROC 0.81 for the viral model.

At enrollment, 65% of viral and 50% of bacterial AFRI patients received antibiotics.

Conclusions
• Host gene expression classifiers performed well in a Sri Lankan population with AFRI, even with non-respiratory pathogens that may not be readily identified.

Antibiotic use was high in patients with viral illnesses.

Host-based diagnostics may play a critical role in improving diagnostic ability and antibiotic use globally.

References

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The signature identified viral infections in 90% and bacterial infections in 83% among patients who were clinically adjudicated as having viral and bacterial infections, respectively [2].

We assessed signature performance in a Sri Lankan cohort admitted with acute febrile respiratory illness (AFRI).

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Using the host immune response for omics-based diagnostics. Immune effector cells (purple) in the peripheral blood directly pathogens using specific receptors (red, bacterial receptor; yellow, virus receptor). Activation of specific receptors by either bacteria (B, green) or virus (V blue) leads to specific receptors (red, virus receptor). Activation of specific receptors (red, virus receptor). Activation of specific receptors (red, virus receptor).