Comparing the Diagnostic Accuracy of Clinician Judgment to a Novel Host Response Diagnostic for Acute Respiratory Illness

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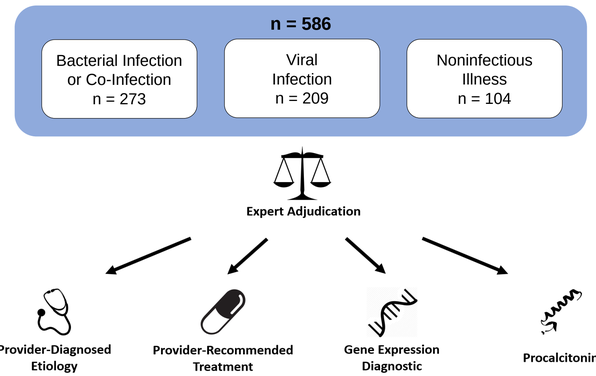
Motivation & Objective

In the United States there are approximately 620 million ambulatory visits for ARI annually, most caused by viral infections.[1,2] Yet, ARI remains difficult to diagnose and is the cause of significant antibiotic misuse.[3] A host gene expression-based diagnostic has the potential to discriminate ARI etiology (bacterial, viral, or non-infectious), to ameliorate this issue.

This study examines a previously-developed rapid multiplex qRT-PCR-based classifier that accurately distinguished bacterial, viral, and noninfectious illness.[4] In this study, we compare the diagnostic accuracy of this BioFire® FilmArray® assay with real-time clinician judgment.

Experimental Design



Methods

A host gene expression biosignature was measured using a RUO BioFire RT-qPCR assay in 586 ED subjects with suspected infection, producing a prediction for bacterial, viral, or non-infectious etiology. Based on chart reviews, we recorded clinical diagnosis as defined both by the provider assessment and by the provider-recommended treatment. The gene expression test, provider diagnosis, provider-recommended treatment, and procalcitonin were compared to clinical adjudication as the reference standard. Bacterial-viral co-infections were treated as bacterial for this study.

We calculated average weighted accuracy (AWA) and change in overall net benefit (ΔNB) where the benefit was based on the appropriate use of antibacterials. For both metrics, we weighted bacterial false negatives four times more seriously than false positives (relative importance r = 0.25) and viral false positives two times more seriously than false negatives (r = 2), values derived from a prior clinician survey.[5] Change in overall net benefit was calculated over a range of estimates for the prevalence of bacterial (10-30%) and viral (50-80%) ARI in the overall population.

Diagnostic Performance

The final cohort (n=586) was 52.6% Female, and 51.4% White, 44.9% Black, and 3.8% other. Mean length of stay was 4.0 days (SD: 7.5 days) among the 51.5% of subjects who were admitted. Clinical adjudication was used as the reference standard to define bacterial, viral, or non-infectious illness.

Table 1: Summary of provider, procalcitonin, and host gene expression test performance. (n = 586)

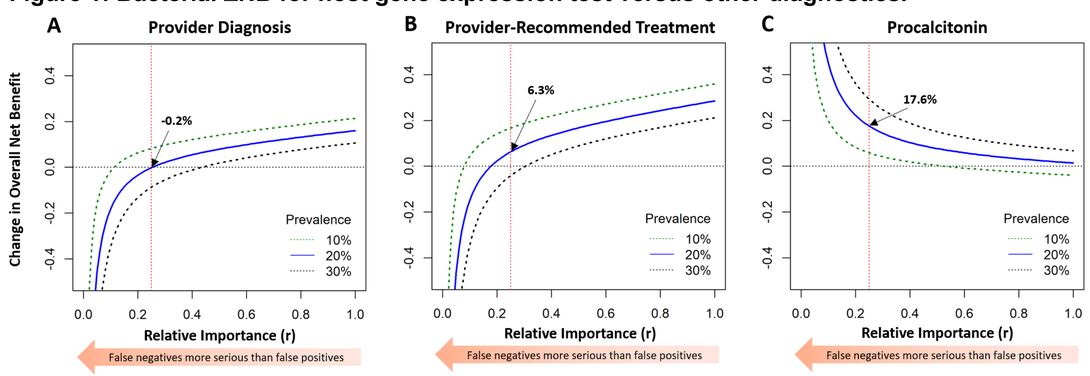
Method	Overall Accuracy	Bacterial Diagnosis			Viral Diagnosis		
		Sensitivity	Specificity	AWA	Sensitivity	Specificity	AWA
Provider Clinical Diagnosis	75.6%	92.7% (89.6-95.8)	67.4% (62.2-72.6)	79.8% (76.7-82.8)	60.8% (54.1-67.4)	95.0% (92.8-97.2)	78.3% (74.9-81.7)
Provider-Recommended Treatment	72.4%	94.5% (91.8-97.2)	59.1% (53.7-64.6)	76.4% (73.4-79.5)	52.6% (45.9-59.4)	96.3% (94.4-98.2)	75.0% (71.6-78.4)
Procalcitonin (n = 582)	72.2%	56.8% (50.9-62.7)	85.5% (81.6-89.4)	71.5% (68.0-75.0)			
Host Gene Expression Test	74.2%	79.1% (74.3-83.9)	80.8% (76.5-85.2)	80.0% †* (76.7-83.2)	76.1% (70.3-81.9)	86.5% (83.0-89.9)	81.4% †‡ (78.1-84.7)

All values are shown with 95% confidence intervals. AWA = Average Weighted Accuracy.
† p < 0.00001 compared to provider-recommended treatment, ‡ p < 0.00001 compared to provider clinical diagnosis, * p < 0.00001 compared to procalcitonin

- The host gene expression test had the highest AWA of all strategies for the diagnosis of both bacterial and viral infection.
- Provider-based diagnoses had the highest sensitivity to bacterial infections at the expense of very low specificity. Conversely, the host gene expression test had the highest sensitivity to viral infections at the expense of a slightly lower specificity.
- Overcalling for bacterial infections and the low specificities associated with the provider-recommended treatment plan resulted in a 33.1% rate of inappropriate antibacterial use. Relying solely on procalcitonin would have reduced this rate to 22.6%, while relying solely on the host gene expression test would have reduced it to 13.9%.

Change in Overall Net Benefit ΔNB for Bacterial Infections

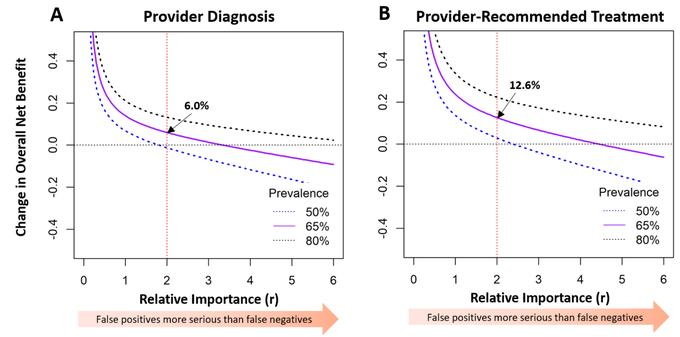
Figure 1: Bacterial ΔNB for host gene expression test versus other diagnostics.



- The host gene expression diagnostic performed comparably in diagnosing bacterial infections with the provider diagnosis in terms of net benefit.
- The host gene expression test provided a net benefit improvement when compared to the provider-recommended treatment and procalcitonin.

ΔNB for Viral Infections

Figure 2: Viral ΔNB for host gene expression test versus other diagnostics.



- The host gene expression diagnostic outperformed providers in terms of net benefit in diagnosing and treating viral infections.

Conclusions

In this cohort, the host gene expression diagnostic performed significantly better than providers in guiding antimicrobial treatment of ARI, providing a net benefit to patients. The diagnostic had higher sensitivity for viral infections and higher specificity for bacterial infections when compared with clinical assessment. It was also superior to procalcitonin. These findings indicate the potential clinical utility of this host gene expression test to reduce the rate of inappropriate antibiotics prescriptions.

Future Directions

- Prospective validation of the host gene expression test to define performance characteristics for the discrimination of bacterial and viral infection.
- Clinical utility study evaluating the impact of real-time host gene expression measurement in guiding antimicrobial treatment in patients with ARI.

Resources:
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